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71 Applicant: Aktiebolaget Hässle  
Kärragatan 5  
S-431 83 Mölndal(SE)

72 Inventor: Carlsson, Enar Ingemar  
Ingegårdsvägen 2C  
S-421 68 Frölunda(SE)

72 Inventor: Junggren, Ulf Krister  
Dammvägen 7  
S-43500 Mölnlycke(SE)

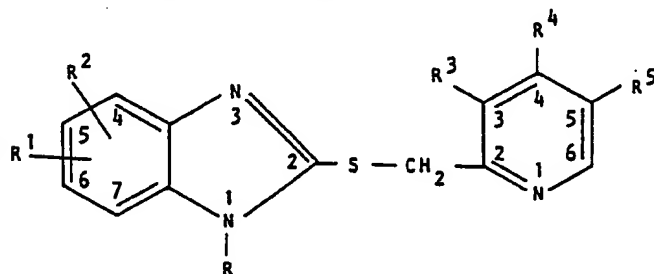
72 Inventor: Larsson, Hakan Sigurd  
Hägalundsvägen 4  
S-430 65 Rävlanda(SE)

72 Inventor: von Wittken Sundell, Gunhild Wika  
Solliden 2  
S-436 00 Askim(SE)

74 Representative: Wurm, Bengt Runio et al,  
Patent and Trade Mark Department Ab Astra  
S-151 85 Södertälje(SE)

54 Novel pharmaceutical compositions.

57 A pharmaceutical preparation containing as active ingredient a compound of the formula



or a therapeutically acceptable salt thereof in which the formula  
 $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , alkyl containing 1-7 carbon atoms, halogen, alkoxy, containing 1-5 carbon atoms, and alkanoyl containing 1-4 carbon atoms.  
 $R$  is selected from the group consisting of H, alkyl

EP 0 074 341 A1

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containing 1-4 carbon atoms, and carboalkoxy containing 2-6 carbon atoms;

and  $R^3$ ,  $R^4$  and  $R^5$ , which are the same or different, are each selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; provided that

a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ;

the use of the compounds for inhibiting gastric acid secretion; compounds included in the formula I, and processes for their preparation.

Novel Pharmaceutical CompositionsDESCRIPTION5 Field of the invention

The object of the present invention is to provide compounds which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the treatment of peptic ulcer.

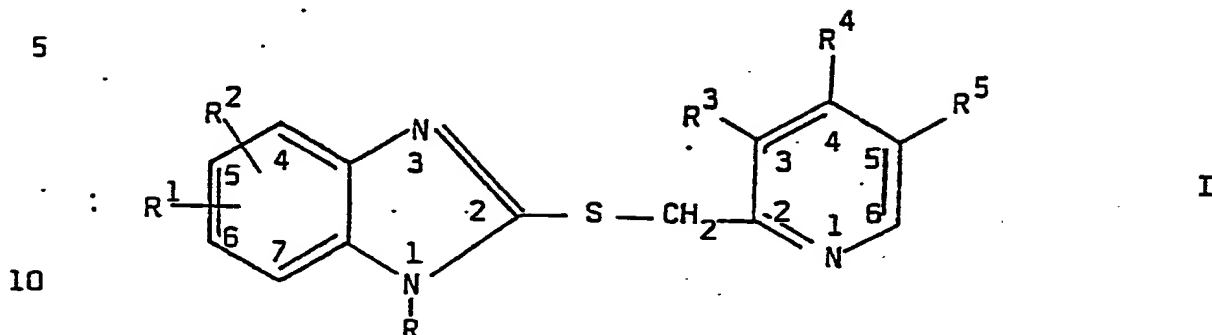
The present invention relates to the use of a group of benzimidazole derivatives, or therapeutically acceptable salts thereof, for inhibiting gastric acid secretion in mammals and man. In a more general sense, the invention relates to the use of the compounds for treatment of gastrointestinal inflammatory diseases in mammals and man, including i.e. gastric and duodenal ulcer. Furthermore it relates to the use of these compounds for treatment of other gastrointestinal disorders, where a gastric anti-secretory effect is desirable i.e. in patients with gastrinomas and in patients with acute upper gastrointestinal bleeding. The invention also relates to pharmaceutical compositions containing at least one member of the said group of benzimidazole derivatives, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to new compounds, and therapeutically acceptable salts thereof, within the said group of benzimidazole derivatives, and to processes for preparation of such new compounds.

Prior art

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the British patent specifications 1 500 043 and 1 525 958, in the US patent 4 182 766 and in the European patent specification No. 0 005 129.

The invention

It has been found that the compounds of the formula



and therapeutically acceptable salts thereof in which formula

15  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , alkyl containing 1-7 carbon atoms, halogen, alkoxy containing 1-5 carbon atoms, and alkanoyl containing 1-4 carbon atoms;

20 R is selected from the group consisting of H, alkanoyl containing 1-4 carbon atoms, and carboalkoxy containing 2-6 carbon atoms;

25 and  $R^3$ ,  $R^4$  and  $R^5$ , which are the same or different, are each selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , provided that

30 a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

35 b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ;

are effective as inhibitors of gastric acid secretion in mammals and man. The compounds of the formula I, and therapeutically acceptable salts thereof, are stable in gastric juice, which is of importance at oral administration.

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Illustrative examples of the radicals in the formula I are:

Alkyl groups  $R^1$  and  $R^2$ : methyl, ethyl, n-propyl, i-propyl,  
10 n-butyl, sec.-butyl, isobutyl, tert.-butyl, n-pentyl, n-hexyl, n-heptyl. It is preferred that alkyl groups  $R^1$  and  $R^2$  contains 1, 2, 3 or 4 carbon atoms. The preferred alkyl group is methyl.

15 Halogen  $R^1$  and  $R^2$ : chloro, bromo, fluoro, iodo. The preferred halogen groups are chloro and bromo.

Alkoxy groups  $R^1$  and  $R^2$ : methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec.-butoxy, isobutoxy, tert.-butoxy,  
20 n-pentoxy. It is preferred that alkoxy groups  $R^1$  and  $R^2$  contain 1, 2 or 3 carbon atoms. The preferred alkoxy group is methoxy.

Alkanoyl groups  $R$ ,  $R^1$  and  $R^2$ :  $\text{HCO-}$ ,  $\text{CH}_3\text{CO-}$ ,  $\text{CH}_3\text{CH}_2\text{CO-}$ ,  
25  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO-}$ ,  $\text{HC}(\text{CH}_3)_2\text{CO-}$ . The preferred alkanoyl group  $R^1$  and  $R^2$  is  $\text{CH}_3\text{CO}$ . The preferred alkanoyl group  $R$  is  $\text{CH}_3\text{CO}$ .

30 Carboalkoxy groups  $R$ :  $\text{CH}_3\text{OC(=O)-}$ ,  $\text{CH}_3\text{CH}_2\text{OC(=O)-}$ ,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OC(=O)-}$ ,  
 $\text{HC}(\text{CH}_3)_2\text{OC(=O)-}$ ,  $\text{CH}_3(\text{CH}_2)_3\text{OC(=O)-}$ ,  $\text{CH}_3(\text{CH}_2)_4\text{OC(=O)-}$ . It is preferred that  
35 carboalkoxy groups  $R$  contains 2 or 3 carbon atoms. Thus, the groups  $\text{CH}_3\text{OCO-}$  and  $\text{CH}_3\text{CH}_2\text{OCO-}$  are preferred.

The preferred meaning of the radical R is H.

Preferred combinations of the radicals in the formula I, subject to the two provisos a) and b) given above, are given in Table 1 below.

Table 1

Preferred combinations of  $R^1$ ,  $R^2$ , R,  $R^3$ ,  $R^4$  and  $R^5$

| $R^1$ and $R^2$ ,<br>the same or different if<br>not indicated otherwise                          | R | $R^3$ , $R^4$ and $R^5$ ,<br>the same or different if<br>not indicated otherwise   |
|---|---|--|
| H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, halogen, alkoxy,<br>alkanoyl | H | H, CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> , OCH <sub>3</sub> ,<br>OC <sub>2</sub> H <sub>5</sub> , OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> |
| H, COOCH <sub>3</sub> , CH <sub>3</sub> , Cl, Br,<br>OCH <sub>3</sub> , CH <sub>3</sub> CO        | H | H, CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> , OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>   |
| H, COOCH <sub>3</sub> , CH <sub>3</sub> , OCH <sub>3</sub> ,<br>CH <sub>3</sub> CO                | H | CH <sub>3</sub> , OCH <sub>3</sub>   |
| H, COOCH <sub>3</sub> , alkyl,<br>alkoxy, alkanoyl  | H | H, CH <sub>3</sub> , OCH <sub>3</sub> , OC <sub>2</sub> H <sub>5</sub>   |
| H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, halogen, alkoxy,<br>alkanoyl | H | $R^3$ : CH <sub>3</sub><br>$R^4$ : OCH <sub>3</sub><br>$R^5$ : CH <sub>3</sub>   |
| H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl          | H | $R^3$ : H<br>$R^4$ : OCH <sub>3</sub><br>$R^5$ : CH <sub>3</sub>   |
| NO <sub>2</sub> , CF <sub>3</sub>   | H | $R^3$ : CH <sub>3</sub><br>$R^4$ : OCH <sub>3</sub><br>$R^5$ : CH <sub>3</sub>   |

| 5  | $R^1$ and $R^2$ ,<br>the same or different if<br>not indicated otherwise                 | R | $R^3$ , $R^4$ and $R^5$ ,<br>the same or different if<br>not indicated otherwise  |
|----|--|---|---|
| 10 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl | H | $R^3$ : CH <sub>3</sub><br>$R^4$ : OCH <sub>3</sub><br>$R^5$ : H  |
| 15 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl | H | $R^3$ : H<br>$R^4$ : OCH <sub>3</sub><br>$R^5$ : H  |
| 20 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl | H | $R^3$ : CH <sub>3</sub><br>$R^4$ : H<br>$R^5$ : CH <sub>3</sub>   |
| 25 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl | H | $R^3$ : H<br>$R^4$ : OCH <sub>3</sub> , OC <sub>2</sub> H <sub>5</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub><br>$R^5$ : H |
| 30 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy<br>alkanyol  | H | $R^3$ : CH <sub>3</sub><br>$R^4$ : CH <sub>3</sub><br>$R^5$ : CH <sub>3</sub>   |

The radicals  $R^1$  and  $R^2$  can be bound to the benzimidazole nucleus in any of the positions 4, 5, 6 and 7 as depicted in formula I. It is preferred that  $R^1$  and  $R^2$  are in position 5 and/or 6.

Preferred individual compounds among those included in the formula I are given in the following Table 2:

Table 2

## Preferred individual compounds

| 5  | R <sup>1</sup>        | R <sup>2</sup>    | R | R <sup>3</sup>  | 4 <sup>4</sup>   | R <sup>5</sup>  |
|----|-----------------------|-------------------|---|-----------------|------------------|-----------------|
|    | 5-OCH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 10 | 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-CH <sub>3</sub>     | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5-OCH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 15 | 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
|    | 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5--COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

20

Further preferred individual compounds are those exemplified in the examples given elsewhere in this specification.

25 In the prior art cited above, no medicinal use is disclosed for the compounds of the formula I. Thus, the present invention comprises pharmaceutical compositions containing a compound of the formula I or a therapeutically acceptable salt thereof as active ingredient, and the use of the compounds  
30 of the formula I or a therapeutically acceptable salt thereof for inhibiting gastric acid secretion in mammals and man.

The compounds of the formula I wherein R<sup>1</sup> and R<sup>2</sup> are as defined above except CF<sub>3</sub> and NO<sub>2</sub>, R is H and R<sup>3</sup>, R<sup>4</sup> and  
35 R<sup>5</sup> are H, CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> are generically disclosed as chemical intermediates in the European patent No. 0 005 129. The specific compounds disclosed in the following Table 3 are disclosed in the said European patent No. 0 005 129.



Table 3

Compounds disclosed in European patent no. 0 005 129.

| 5 | R | R <sup>1</sup>      | R <sup>2</sup>    | R <sup>3</sup>  | R <sup>4</sup>  | R <sup>5</sup>  | Remark        |
|---|---|---------------------|-------------------|-----------------|-----------------|-----------------|---------------|
|   | H | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H               | CH <sub>3</sub> | CH <sub>3</sub> | base          |
|   | H | 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | CH <sub>3</sub> | H               | CH <sub>3</sub> | hydrochloride |
|   | H | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | base          |

10

The present invention, in so far as it concerns compounds of the formula I by themselves, their pharmaceutically acceptable salts, and processes for their preparations, relates to

15

i) the compounds of the formula I wherein R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is C<sub>2</sub>H<sub>5</sub>

20

ii) the compounds of the formula I wherein R is alkanoyl or carboalkoxy

iii) the compounds of the formula I wherein R is H except the compounds wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are combined as follows:

25

|    | R <sup>1</sup>      | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>  | R <sup>5</sup>  |
|----|---------------------|-------------------|---|-----------------|-----------------|-----------------|
|    | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub> | CH <sub>3</sub> |
|    | 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H               | CH <sub>3</sub> |
| 30 | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> |

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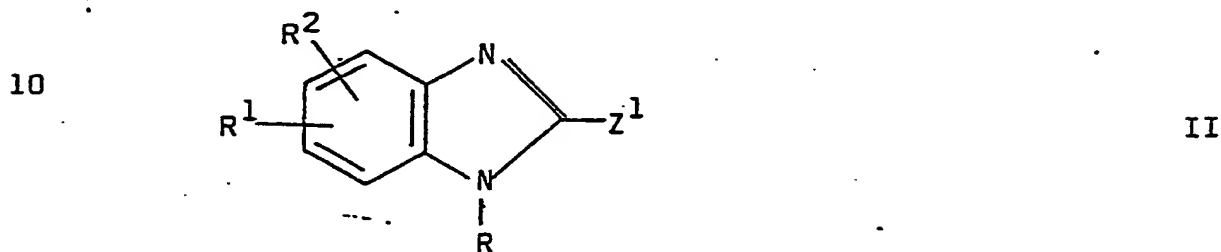
iv) the compounds of the formula I wherein R<sup>1</sup> and/or R<sup>2</sup> are CF<sub>3</sub> or NO<sub>2</sub>.

The preferred compounds within the groups i), ii), iii) and iv) will comprise the same compounds that are indicated as preferred in Table 1 and Table 2 above, subject to the

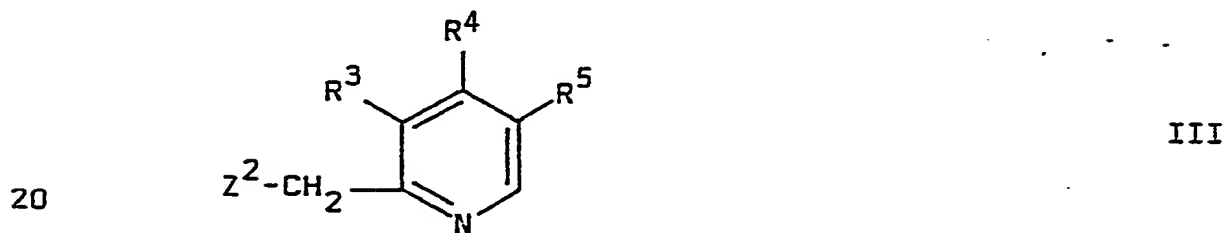
proviso that the specific compounds listed in Table 3 are excluded.

The compounds of the formula I can be prepared by known methods such as

A. reacting a compound of the formula



15 with a compound of the formula



in which formulas R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined previously and wherein one of Z<sup>1</sup> and Z<sup>2</sup> is SH and the other is a leaving group.

25 Examples of leaving groups Z<sup>1</sup> and Z<sup>2</sup> in the compounds II and III are halogens, preferably chlorine, bromine or iodine, acyl radicals, for example, residues of strong organic sulfonic acids, for instance, of an arylsulfonic acid, for example, tosyloxy, or an alkylsulfonic acid, for example, mesyloxy; alkylmercapto groups, for example, methylmercapto; alkylsulfinyl groups, for example, methylsulfinyl and the like.

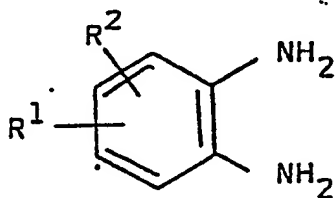
35 Thus, Z<sup>1</sup> or Z<sup>2</sup> when designating leaving groups may be a reactive esterified hydroxy group.

The reaction of a compound of formula II above with a compound of formula III is conveniently carried out in the presence of a suitable solvent that is inert under the reaction conditions utilized as described hereinafter. The reaction may further be carried out in the presence of a suitable base. Suitable bases include, for example, inorganic bases such as sodium or potassium hydroxide, sodium or potassium hydride and the like, organic bases such as tertiary amines, for example, triethylamine and the like.

Suitable solvents for the above described reaction include, for example, alcohols, preferably lower alkanols such as, methanol and ethanol; mixtures of such alcohols with water, ethers, such as, tetrahydrofuran; halogenated hydrocarbons, such as, methylene chloride and chloroform, and the like.

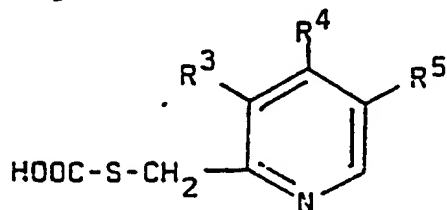
The reaction of the compounds of formulas II and III may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture. It is preferred to carry out the reaction, however, at a temperature at or close to the boiling point of the reaction mixture for the preparation of a compound of the formula I wherein R is H;

B. reacting a compound of the formula



IV

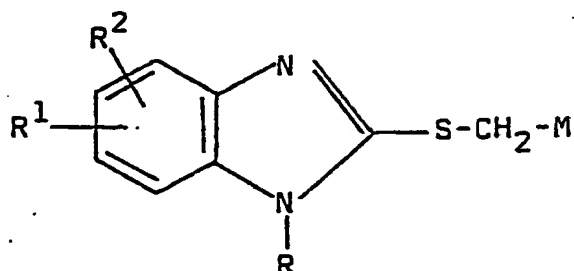
wherein  $\text{R}^1$  and  $\text{R}^2$  have the same meaning as given above with a compound of the formula



V

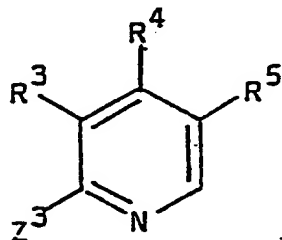
wherein  $R^3$ ,  $R^4$  and  $R^5$  have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

5 C. reacting a compound of the formula



VI

wherein R,  $R^1$  and  $R^2$  have the meaning given above and M is K, Na or Li, with a compound of formula

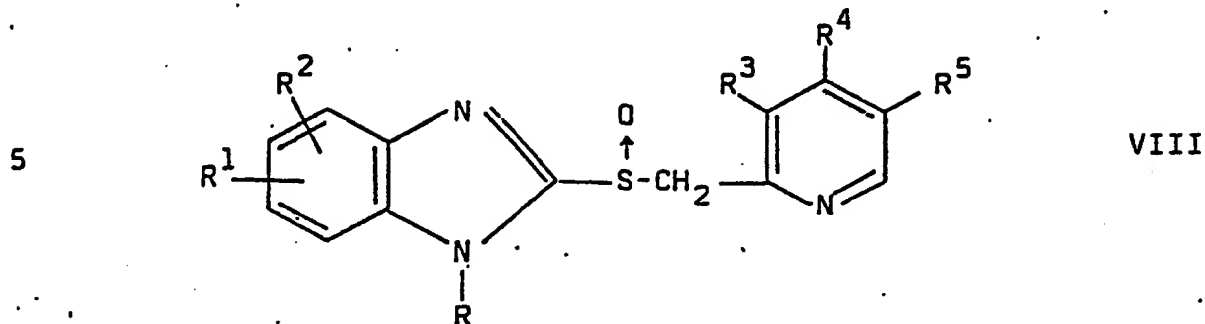


VII

wherein  $R^3$ ,  $R^4$  and  $R^5$  have the meaning given above and  $Z^3$  is a reactive esterified hydroxy group, to the formation of a compound of the formula I.

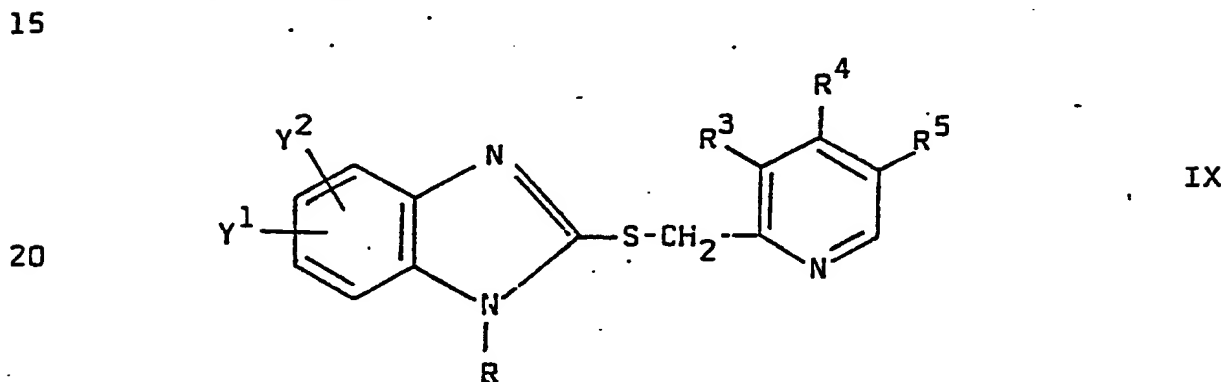
25 The reactive esterified hydroxy group  $Z^3$  may, as in the case of  $Z^1$  and  $Z^2$ , be a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, or esterified with sulfuric acid or  
 30 with a strong organic sulfonic acid such as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

D. reduction of a compound of the formula

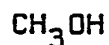


10 to the formation of a compound of the formula I:

E. for the preparation of a compound of the formula I wherein the radicals  $R^1$  and/or  $R^2$  is  $\text{COOCH}_3$  or  $\text{COOC}_2\text{H}_5$ , reacting a compound of the formula

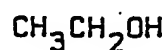


wherein  $R$ ,  $R^3$ ,  $R^4$  or  $R^5$  are as defined above and wherein  $Y^1$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, and  $Y^2$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, or  $R^1$ , with



X

or



XI

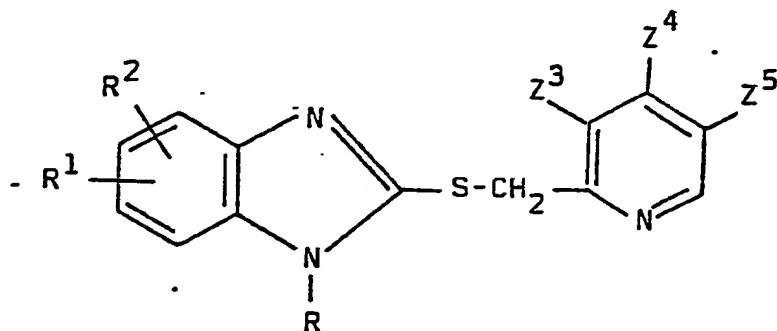
35 or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein  $R^1$  and/or  $R^2$  is  $\text{CH}_3\text{COO}$  or  $\text{CH}_3\text{CH}_2\text{COO}$ .

This reaction is an ordinary esterification which is carried out in customary manner.

Functionally equivalent derivatives of the hydroxy group in the compounds X and XI are for example halogen such as Cl or Br, or  $-N_2$ .

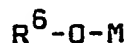
Functionally equivalent derivatives of the carboxyl group  $Y^1$  and  $Y^2$  are for example a metal carboxylate group or an activated carboxyl group, in which case the radicals  $Y^1$  or  $Y^2$  are for example an acid chloride, an alkyl ester, an acid anhydride or a mixed anhydride with formic esters or carboxylic acids, sulphonic or inorganic esters or derivatives obtained by a reaction between a carboxylic acid and a carbodiimide or similarly functioning compounds such as  $N_1N^1$ -carbonyldiimidazole or N-ethyl-5-phenylisoxazolium-3<sup>1</sup>-sulphonate, the derivative of the carboxyl group  $Y^1$  or  $Y^2$  being a metal carboxylate group when the hydroxyl group in the compounds X or XI is replaced with halogen. A further functionally equivalent derivative of the carboxyl groups  $Y^1$  and  $Y^2$  is the group  $-CN$ , in which case a cyanide is reacted with a compound of the formula X or XI with subsequent hydrolysis to give a compound of the formula I wherein  $R^1$  and/or  $R^2$  is  $CH_3COO$  or  $CH_3CH_2COO$ .

F. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ , reacting a compound of the formula



XII

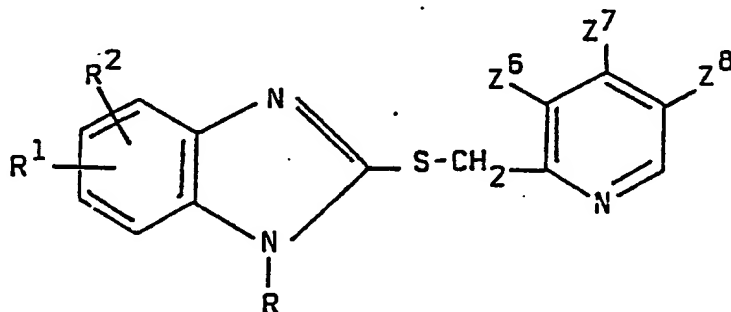
wherein  $R$ ,  $R^1$  and  $R^2$ , are as defined above and  $Z^3$ ,  $Z^4$  and  $Z^5$  represent either  $R^3$ ,  $R^4$  and  $R^5$ , respectively, or halogen such as Cl, Br, F or I, or  $\text{NO}_2$ , whereby at least one of  $Z^3$ ,  $Z^4$  and  $Z^5$  represents halogen or  $\text{NO}_2$ , with a compound of



XIII

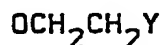
wherein  $R^6$  is  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_3$  or  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , and  $M$  is Na, K, or Li, to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ;

G. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , reacting a compound of the formula



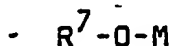
XIV

wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above, and  $Z^6$ ,  $Z^7$  and  $Z^8$  represent either  $R^3$ ,  $R^4$  and  $R^5$ , respectively, or a radical



XV

where  $Y$  is halogen, whereby at least one of  $Z^6$ ,  $Z^7$  and  $Z^8$  represent  $\text{OCH}_2\text{CH}_2\text{Y}$ , with a compound of the formula

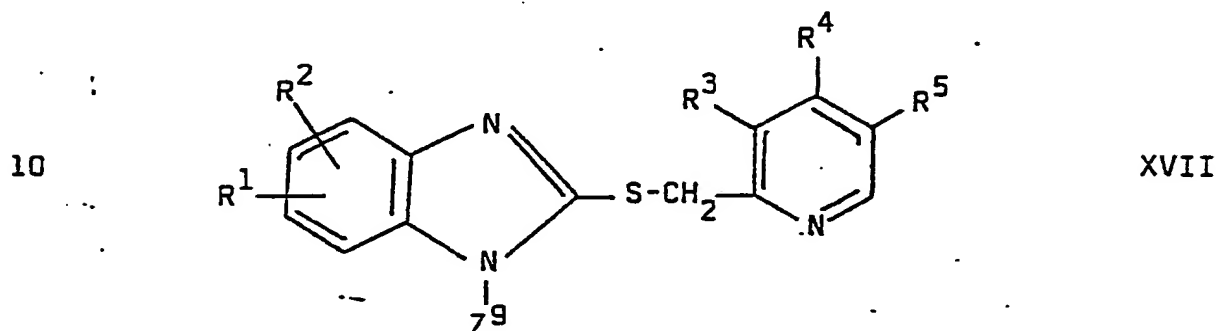


XVI

wherein  $R^7$  is  $\text{CH}_3$  or  $\text{CH}_2\text{CH}_3$  and  $M$  is Na, K or Li, to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ .

Method F and Method G represent the known Williamson ether synthesis and is carried out in known manner.

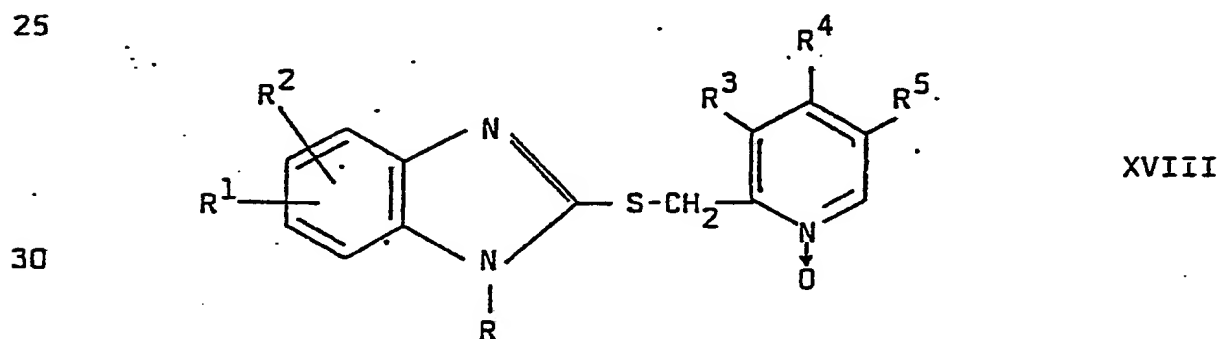
H. for the preparation of a compound of the formula I  
5 wherein R is H, hydrolyzing a compound of the formula



15 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $Z^9$  is an alkanoyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein R is H.

20 The radical  $Z^9$  can be an alkanoyl group containing 1-6 carbon atoms or a carboalkoxy group containing 2-6 carbon atoms.

I. reduction of a compound of the formula

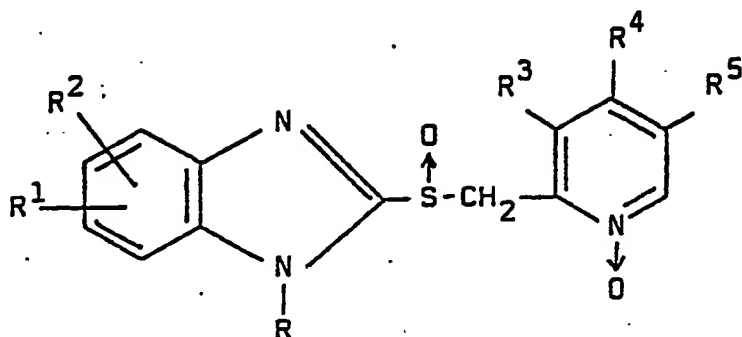


to the formation of a compound of the formula I.

35



J. reduction of a compound of the formula



XIX

to the formation of a compound of the formula I.

Depending on the process conditions and the starting materials, the end product of the formula I is obtained either as the free base or as a salt. Both the free base and the salts of the end products are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. Acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. The free bases obtained may also form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfonic acid, phosphoric acid, nitric acid, and perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, salicylic acid or p-aminosalicylic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid, naphthyl-

sulfonic acid or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered in higher purity from a new salt solution.

10 The starting materials utilized in the processes A-J are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the active compounds of the formula I will normally be administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains the active component either in the form of free base or in the form of a pharmaceutically acceptable, non-toxic salt, as described earlier, optionally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. The compounds may also be used without carrier material. Usually the amount of active compound is between 0.1 and 99% by weight of the preparation, for example between 0.5 to 20% by weight in preparations for injection and between 2 and 50% by weight in preparations for oral administration.

30 In the preparation of pharmaceutical preparations containing a compound of the formula I in the form of dosage units for oral administration, the active compound may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, a starch such as potatoe starch, corn starch, or amylopectin, cellulose derivatives or gelatin, and may also include a lubricant such as magnesium stearate, calcium

stearate or polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, a core prepared as described above may be coated with a concentrated sugar solution which may contain gum arabic, gelatin, talc, titanium dioxide or alternatively with a lacquer dissolved in volatile organic solvents or mixtures of solvents. To this coating various dyes may be added in order to distinguish tablets with different active compounds or with different amounts of the active compound present.

10

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

20

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in admixture with a neutral fatty base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in admixture with a vegetable oil or with paraffin oil.

25

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2% to 20% by weight of the active ingredient, the remainder comprising for example sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

35

Solutions for parenteral administration by injection may be prepared as sterile solution, for example in pyrogen-free

water, of a water soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be  
5 manufactured in different dosage unit ampoules.

The dosage at which the active substance are administered may vary within a wide range and will depend on various factors such as for example the individual requirements of  
10 each patient and the manner of administration. In general, oral dosages will be in the range from 100 to 400 mg/day of active substance and intravenous dosages in a range from 5 to 20 mg/day.

15 The invention is illustrated by the following examples.

Example 1. Method A. Preparation of 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-5-COCH<sub>3</sub>-6-CH<sub>3</sub>-benzimidazole

20 22.2 g (0.1 mole) of 3,5-dimethyl-4-methoxy-2-chloromethylpyridine hydrochloride and 20.6 g (0.1 mole) of 5-COCH<sub>3</sub>-6-CH<sub>3</sub>-2-mercapto benzimidazole was dissolved in 250 ml methanol whereafter 4 g (0.1 mole) NaOH dissolved in 25 ml H<sub>2</sub>O was added. The mixture was heated to reflux and  
25 an additional amount of 4 g (0.1 mole) NaOH in 25 ml H<sub>2</sub>O was added dropwise during 15 min. The mixture was thereafter refluxed during 6 hours whereafter it was cooled and diluted with 500 ml H<sub>2</sub>O. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried and evaporated. The remainder was recrystal-  
30 lized from acetonitrile giving the title substance in the form of free base. Yield: 30 g (85% of the theoretical yield). M.P.: 139°C.

Examples 2-50

5

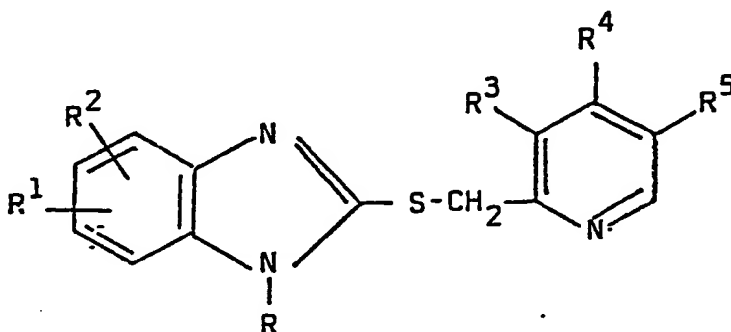
The compounds identified by example numbers 2-50 in the following Table 4 were prepared using the same method of preparation as in Example 1. The compounds were obtained in the form of their free base. The compound of Example 1  
10 is also included in the table.

Table 4

Identifying data for compounds of the invention

15

20



| Example<br>no | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  | M.p.<br>°C |
|---------------|----------------------|-------------------|---|-----------------|------------------|-----------------|------------|
| 1             | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> | 148        |
| 2             | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> | 125        |
| 3             | 5-COOCH <sub>3</sub> | H                 | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> | 136        |
| 4             | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | H               | 140        |
| 5             | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | H               | 170 (oil)  |
| 6             | 4-CH <sub>3</sub>    | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H                | CH <sub>3</sub> | 206        |
| 7             | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H                | CH <sub>3</sub> | 125        |
| 8             | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> | 100 (oil)  |
| 9             | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               | 97         |
| 10            | 4-CH <sub>3</sub>    | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               | 110        |

cont..

| Example<br>no | R <sup>1</sup>                      | R <sup>2</sup>    | R | R <sup>3</sup>   | R <sup>4</sup>                                  | R <sup>5</sup>  | M. p.<br>°C |
|---------------|-------------------------------------|-------------------|---|------------------|---|-----------------|-------------|
| 11            | 5-COCH <sub>3</sub>                 | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 139         |
| 12            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | H   | CH <sub>3</sub> | 130         |
| 13            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | CH <sub>3</sub>                                 | CH <sub>3</sub> | 184         |
| 14            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | H                | OCH <sub>3</sub>                                | H               | 146         |
| 15            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | H                | OC <sub>2</sub> H <sub>5</sub>                  | H               | 90-94       |
| 16            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | H               | 160         |
| 17            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 119         |
| 18            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | H                | OCH <sub>3</sub>                                | CH <sub>3</sub> | 184         |
| 19            | 5-COOCH <sub>3</sub>                | H                 | H | CH <sub>3</sub>  | H   | CH <sub>3</sub> | 130         |
| 20            | 5-COOCH <sub>3</sub>                | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 175         |
| 21            | 5-COCH <sub>3</sub>                 | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 122-124     |
| 22            | 5-OCH <sub>3</sub>                  | H                 | H | H                | OCH <sub>3</sub>                                | CH <sub>3</sub> | 168         |
| 23            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 110-119     |
| 24            | 5-CH <sub>3</sub>                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 148         |
| 25            | H                                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 125         |
| 26            | 5-Cl                                | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 180         |
| 27            | 5-CH <sub>3</sub>                   | H                 | H | H                | OC <sub>2</sub> H <sub>4</sub> OCH <sub>3</sub> | H               | 100         |
| 28            | 5-COOC <sub>2</sub> H <sub>5</sub>  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> | 130         |
| 29            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | CH <sub>3</sub>                                 | CH <sub>3</sub> | 157         |
| 30            | CH <sub>3</sub>                     | CH <sub>3</sub>   | H | CH <sub>3</sub>  | CH <sub>3</sub>                                 | H               | 140         |
| 31            | COOCH <sub>3</sub>                  | CH <sub>3</sub>   | H | CH <sub>3</sub>  | H   | CH <sub>3</sub> | 125         |
| 32            | 5-C(CH <sub>3</sub> ) <sub>3</sub>  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 33            | 5-NO <sub>2</sub>                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 34            | 5-CH <sub>3</sub>                   | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 35            | 4-CH <sub>3</sub>                   | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 36            | 5-C <sub>2</sub> H <sub>5</sub>     | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 37            | 5-CF <sub>3</sub>                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 38            | 5-CH(CH <sub>3</sub> ) <sub>2</sub> | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 39            | 5-Cl                                | 6-Cl              | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 40            | 5-OC <sub>2</sub> H <sub>5</sub>    | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 41            | 5-Br                                | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                | CH <sub>3</sub> |             |
| 42            | 5-OCH <sub>3</sub>                  | H                 | H | OCH <sub>3</sub> | H   | H               | cont.       |

| Example<br>no | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>                 | R <sup>5</sup>                |
|---------------|----------------------|-------------------|---|-----------------|--------------------------------|-------------------------------|
| 43            | 5-Cl                 | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>                | H                             |
| 44            | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>                | H                             |
| 45            | 5-CH <sub>3</sub>    | 7-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | H                             |
| 46            | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub>               | H                             |
| 47            | 5-COOCH <sub>3</sub> | 7-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | H                             |
| 48            | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>                | H                             |
| 49            | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OC <sub>2</sub> H <sub>5</sub> | CH <sub>3</sub>               |
| 50            | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub>               | C <sub>2</sub> H <sub>5</sub> |

Identifying data for the compounds according to examples 32-50 are given in the following table 5.

Table 5. NMR data for compounds of the invention

| Compound according<br>to example no. | NMR data<br>$\delta$   |
|--------------------------------------|--|
| 32                                   | 1.37 (s, 9H), 2.26 (s, 3H), 2.30 (s, 3H),<br>3.76 (s, 3H), 4.37 (s, 2H), 7.25 (k, 1H),<br>7.49 (d, 1H), 7.57 (d, 1H), 8.30 (s, 1H) |
| 33                                   | 2.21 (s, 3H), 2.31 (s, 3H), 3.75 (s, 3H),<br>4.77 (s, 2H), 7.64 (d, 1H), 8.11 (k, 1H),<br>8.23 (s, 1H), 8.36 (d, 1H)               |

cont.

Table 5. NMR data for compounds of the invention.  
continued

| Compound according<br>to example no. | NMR-data<br>$\delta$   |
|--------------------------------------|--|
| 34                                   | 2.23 (s,3H), 2.28 (s,3H), 2.33 (s,6H),<br>3.75 (s,3H), 4.33 (s,2H), 7.29 (s,2H),<br>8.23 (s,1H)  |
| 35                                   | 2.28 (s,3H), 2.33 (s,3H), 2.43 (s,3H),<br>2.58 (s,3H), 3.81 (s,3H), 4.42 (s,2H),<br>6.92 (s,1H), 7.29 (s,1H), 8.36 (s,1H)                              |
| 36                                   | 1.25 (t,3H), 2.25 (s,3H), 2.30 (s,3H),<br>2.72 (k,2H), 3.76 (s,3H), 4.38 (s,2H),<br>7.02 (k,1H), 7.35 (d,1H), 7.45 (d,1H),<br>8.26 (s,1H)              |
| 37                                   | 2.31 (s,3H), 2.35 (s,3H), 3.84 (s,3H),<br>4.46 (s,2H), 7.51 (k,1H), 7.70 (d,1H),<br>7.92 (d,1H), 8.38 (s,1H)   |
| 38                                   | 1.25 (s,3H), 1.33 (s,3H), 2.27 (s,3H),<br>2.33 (s,3H), 3.03 (m,1H), 3.80 (s,3H),<br>4.51 (s,2H), 7.17 (k,1H), 7.53 (d,1H),<br>7.58 (d,1H), 8.36 (s,1H) |
| 39                                   | 2.22 (s,3H), 2.31 (s,3H), 3.81 (s,3H),<br>4.72 (s,2H), 7.76 (s,2H), 8.23 (s,1H)  |
| 40                                   | 1.41 (t,3H), 2.30 (s,3H), 2.35 (s,3H),<br>3.82 (s,3H), 4.10 (k,2H), 4.39 (s,2H),<br>6.92 (k,1H), 7.14 (d,1H), 7.52 (d,1H),<br>8.40 (s,1H)              |

cont.



Table 5. NMR data for compounds of the invention.  
continued

| Compound according<br>to example no. | NMR data<br>$\delta$  |
|--------------------------------------|---|
| 41                                   | 2.16 (s,3H), 2.26 (s,3H), 3.71 (s,3H),<br>4.68 (s,2H), 7.23 (k,1H), 7.43 (d,1H),<br>7.65 (d,1H), 8.18 (s,1H)              |
| 42                                   | 3.80 (s,3H), 3.83 (s,3H), 4.50 (s,2H),<br>6.90 (k,1H), 7.15 (d,1H), 7.24 (m,2H),<br>7.53 (d,1H), 8.23 (k,1H)              |
| 43                                   | 2.33 (s,3H), 2.35 (s,3H), 4.80 (s,2H),<br>7.19 (m,2H), 7.52 (d,1H), 7.58 (d,1H),<br>8.34 (d,1H)                           |
| 44                                   | 2.34 (s,6H), 3.85 (s,3H), 4.51 (s,2H),<br>6.89 (k,1H), 7.15 (d,1H), 7.15 (d,1H),<br>7.53 (d,1H), 8.41 (d,1H)              |
| 45                                   | 2.16 (s,6H), 2.38 (s,3H), 2.53 (s,3H),<br>4.46 (s,2H), 6.86 (s,1H), 6.99 (d,1H),<br>7.25 (s,1H), 8.20 (d,1H)              |
| 46                                   | 2.26 (s,3H), 3.86 (s,3H), 3.91 (s,3H),<br>4.70 (s,2H), 6.87 (m,2H), 7.10 (d,1H),<br>7.48 (d,1H), 8.42 (d,1H)              |
| 47                                   | 2.36 (s,6H), 2.65 (s,3H), 3.97 (s,3H),<br>4.50 (s,2H), 7.17 (d,1H), 7.84 (s,1H),<br>8.24 (s,1H), 8.41 (d,1H),             |
| 48                                   | 2.31 (s,3H), 2.34 (s,3H), 2.64 (s,3H),<br>4.71 (s,2H), 7.12 (d,1H), 7.59 (d,1H),<br>7.91 (k,1H), 8.22 (d,1H), 8.36 (d,1H) |

cont.

Table 5. NMR data for compounds of the invention.  
continued

| 5  | Compound according<br>to example no. | NMR data<br>$\delta$  |
|----|--------------------------------------|---|
| 10 | 49                                   | 1.41 (t,3H), 2.27 (s,3H), 2.31 (s,3H),<br>3.87 (s,3H); 3.94 (k,2H), 4.41 (s,2H),<br>6.89 (k,1H), 7.12 (d,1H), 7.50 (d,1H),<br>8.35 (s,1H) |
| 15 | 50                                   | 1.17 (t,3H), 2.61 (k,2H), 2.69 (s,3H),<br>3.93 (s,6H), 4.43 (s,2H), 7.00 (s,1H),<br>7.45 (s,1H), 8.26 (s,1H), 8.35 (s,1H) -               |

The starting materials in the examples 1-50 were prepared in accordance with the following:

- 20 1) a substituted o-phenylenediamine was reacted with potassium etylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a corresponding substituted 2-mercaptobenzimidazole;
- 25 2) a substituted 2-chloromethylpyridine was prepared by reacting the corresponding 2-hydroxymethylpyridine with thionylchloride;
- 30 3) a substituted 2-chloromethylbenzimidazole was prepared by condensing the o-phenylenediamine with chloroacetic acid.

The following examples illustrate how the compounds of the formula I can be incorporated in pharmaceutical compositions:

Example 51. Syrup

5

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

|    |  |         |
|----|--|---------|
|    | 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-                   |         |
| 10 | -(5-acetyl-6-methyl)benzimidazole · HCl                            | 2.0 g   |
|    | Saccharin  | 0.6 g   |
|    | Sugar  | 30.0 g  |
|    | Glycerin   | 5.0 g   |
|    | Flavouring agent   | 0.1 g   |
| 15 | Ethanol 96%  | 10.0 ml |
|    | Distilled water (sufficient to obtain a final<br>volume of 100 ml) |         |

20 Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

25 The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 52. Tablets

30 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-(5-methoxy)-benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10% solution of gelatin and was ground through a 12-mesh sieve. After drying, potato  
35 starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into

tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

5 Example 53. Tablets

Granules were prepared from 2-[2-(3,5-dimethyl-4-methoxy)-  
pyridylmethylthio]-(5-carbomethoxy-6-methyl)benzimidazole  
base (250 g), lactose (175.9 g) and an alcoholic  
10 solution of polyvinylpyrrolidone (25 g). After drying,  
the granules were mixed with talc (25 g), potato starch  
(40 g), and magnesium stearate (2.50 g) and were  
pressed into 10.000 tablets. These tablets are first coated  
with a 10% alcoholic solution of shellac and thereupon with  
15 an aqueous solution containing saccharose (45%), gum arabic  
(5%), gelatin (4%), and dyestuff (0.2%). Talc and powdered  
sugar were used for powdering after the first five coatings.  
The coating was then covered with a 66% sugar syrup and  
polished with a solution of 10% carnauba wax in carbon  
20 tetrachloride.

Example 54. Solution for injection

2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-(5-acetyl-6-  
25 -methyl)benzimidazole hydrochloride (1 g), sodium chloride  
(0.6 g) and ascorbic acid (0.1 g) were dissolved in  
sufficient amount of distilled water to give 100 ml of  
solution. This solution, which contains 10 mg of active  
substance for each ml, was used in filling ampoules, which  
30 were sterilized by heating at 120°C for 20 minutes.

Biological testsGastric acid secretion inhibiting effect on conscious dogs5 Test Method

Chronic gastric fistula dogs (Heidenhain pouch dogs) were used. These dogs have been surgically provided with a gastric cannula in the pouch. Following a 4 weeks' recovery  
10 period after surgery, tests were performed once a week on each dog. Food and water were withdrawn 18 hours before each test.

Gastric acid secretion was induced by continuous infusion  
15 of histamine at individual doses (100-300  $\mu\text{mol/kg, h}$ ), resulting in submaximal secretion of gastric acid. At least 2 hours after onset of stimulation, when the gastric acid secretion had reached a steady level, the test compounds in the form of free base suspended in 0.5% Methocel<sup>®</sup>  
20 (90 HG, 15.000, Dow Chem. corp.), were given orally by stomach tube. The gastric juice was collected by free flow from the gastric cannula in consecutive 30 minutes samples for 3 hours. The samples were titrated to pH 7.0 with 0.1 M NaOH using a Radio-meter automatic titrator and  
25 the acid output was calculated.

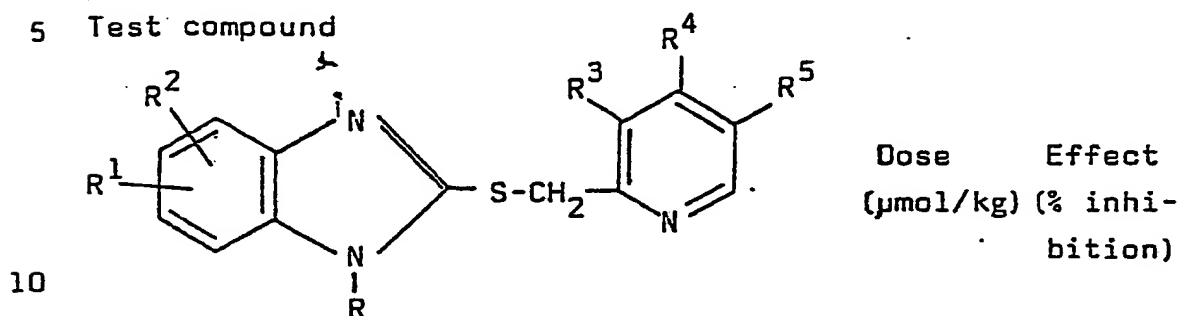
The per cent inhibition of acid secretion was calculated by comparing in each dog the acid output in the tests to the acid output in control tests when only the vehicle was  
30 given.

The test results are given in Table 6 below.

Table 6

Gastric acid secretion inhibiting effect on conscious dogs

5 Test compound



|    | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |   |    |
|----|----------------------|-------------------|---|-----------------|------------------|-----------------|---|----|
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 2 | 75 |
| 15 | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 8 | 50 |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 2 | 80 |
|    | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 2 | 35 |
|    | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 8 | 90 |
|    | 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> | 2 | 60 |
| 20 | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> | 8 | 80 |
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> | 2 | 75 |

25

Comment to the test results

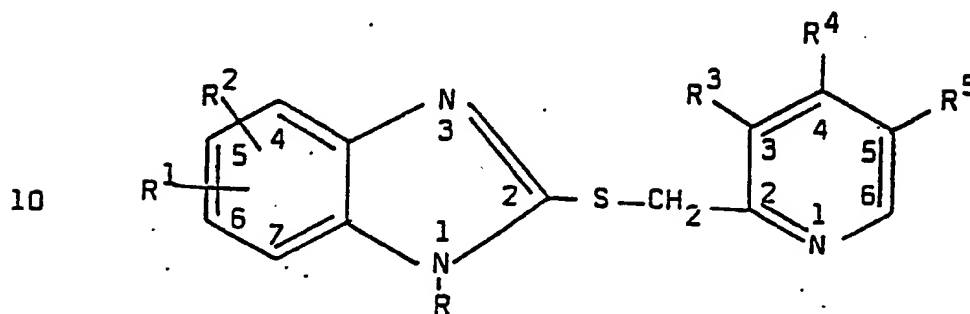
It is seen in Table 6 that the tested compounds after oral administration exhibited a high inhibiting effect on the gastric secretion.

30

What we claim is:

1. A pharmaceutical preparation containing as active ingredient a compound of the formula

5



15 or a therapeutically acceptable salt thereof, in which formula

$R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , alkyl containing 1-7 carbon atoms, halogen, alkoxy containing 1-5 carbon atoms, and alkanoyl containing 1-4 carbon atoms;

20

R is selected from the group consisting of H, alkanoyl containing 1-4 carbon atoms, and carboalkoxy containing 2-6 carbon atoms;

25

and  $R^3$ ,  $R^4$  and  $R^5$ , which are the same or different, are each selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; provided that

30 a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

35 b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ;

optionally in association with a pharmaceutically acceptable carrier.

2. A pharmaceutical preparation according to claim 1,  
5 containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, halogen, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbon atoms; R is H;  
10 and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$ , and  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ .
3. A pharmaceutical preparation according to claim 1,  
20 containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{CH}_3$ , Cl, Br,  $\text{OCH}_3$  and  $\text{CH}_3\text{CO}$ ; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting  
20 of H,  $\text{CH}_3$ ,  $\text{OCH}_3$ , and  $\text{OCH}_2\text{CH}_2\text{OCH}_3$ .
4. A pharmaceutical preparation according to claim 1,  
containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each  
25 selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{CH}_3$ ,  $\text{OCH}_3$ , and  $\text{CH}_3\text{CO}$ ; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of  $\text{CH}_3$  and  $\text{OCH}_3$ .
- 30 5. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ , alkyl having 1-4 carbon atoms, alkoxy having 1-3 carbon atoms,  
35 and alkanoyl having 1-4 carbon atoms; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of H,  $\text{CH}_3$ ,  $\text{OCH}_3$ , and  $\text{OC}_2\text{H}_5$ .



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6. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, halogen, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbon atoms; R is H; and wherein  $R^3$  is  $\text{CH}_3$ ;  $R^4$  is  $\text{OCH}_3$  and  $R^5$  is  $\text{CH}_3$ .
7. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbon atoms; R is H; and wherein  $R^3$  is H,  $R^4$  is  $\text{OCH}_3$  and  $R^5$  is  $\text{CH}_3$ .
8. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbons atoms; R is H; and wherein  $R^3$  is  $\text{CH}_3$ ,  $R^4$  is  $\text{OCH}_3$  and  $R^5$  is H.
9. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbon atoms; R is H; and wherein  $R^3$  is H,  $R^4$  is  $\text{OCH}_3$  and  $R^5$  is H.
10. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl having 1-4 carbon atoms; R is H; and wherein  $R^3$  is  $\text{CH}_3$ ,  $R^4$  is H and  $R^5$  is  $\text{CH}_3$ .

11. A pharmaceutical preparation according to claim 1,  
 containing as active ingredient a compound of the formula I  
 wherein  $R^1$  and  $R^2$  are the same or different and each selected  
 from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having  
 5 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl  
 having 1-4 carbon atoms; R is H, and wherein  $R^3$  is H,  $R^4$  is  
 $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , and  $R^5$  is H.

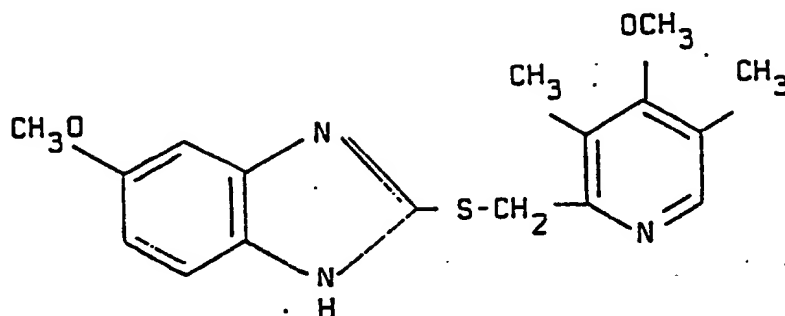
12. A pharmaceutical preparation according to claim 1,  
 10 containing as active ingredient a compound of the formula I  
 wherein  $R^1$  and  $R^2$  are the same or different and each selected  
 from the group consisting of H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , alkyl having  
 1-4 carbon atoms, alkoxy having 1-3 carbon atoms, and alkanoyl  
 having 1-4 carbon atoms; R is H; and wherein  $R^3$  is  $\text{CH}_3$ ,  $R^4$  is  
 15  $\text{CH}_3$ , and  $R^5$  is  $\text{CH}_3$ .

13. A pharmaceutical preparation according to claim 1,  
 containing as active ingredient a compound of the formula I  
 wherein R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are combined as follows:

20

|    | $R^1$              | $R^2$            | R | $R^3$         | $R^4$          | $R^5$         |
|----|--------------------|------------------|---|---------------|----------------|---------------|
| 25 | $5\text{-OCH}_3$   | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | $5\text{-COOCH}_3$ | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | $5\text{-COOCH}_3$ | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | $5\text{-COCH}_3$  | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | $5\text{-COOH}_3$  | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
| 30 | $5\text{-CH}_3$    | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | $5\text{-COCH}_3$  | 6- $\text{CH}_3$ | H | H             | $\text{CH}_3$  | $\text{CH}_3$ |
|    | $5\text{-OCH}_3$   | H                | H | $\text{CH}_3$ | $\text{CH}_3$  | $\text{CH}_3$ |
|    | $5\text{-COCH}_3$  | 6- $\text{CH}_3$ | H | H             | $\text{OCH}_3$ | H             |
|    | $5\text{-COOCH}_3$ | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | H             |
| 35 | $5\text{-COCH}_3$  | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{CH}_3$  | $\text{CH}_3$ |
|    | $5\text{-COOCH}_3$ | 6- $\text{CH}_3$ | H | H             | $\text{OCH}_3$ | H             |

14. A pharmaceutical composition according to claim 1, containing as active ingredient a compound of the formula



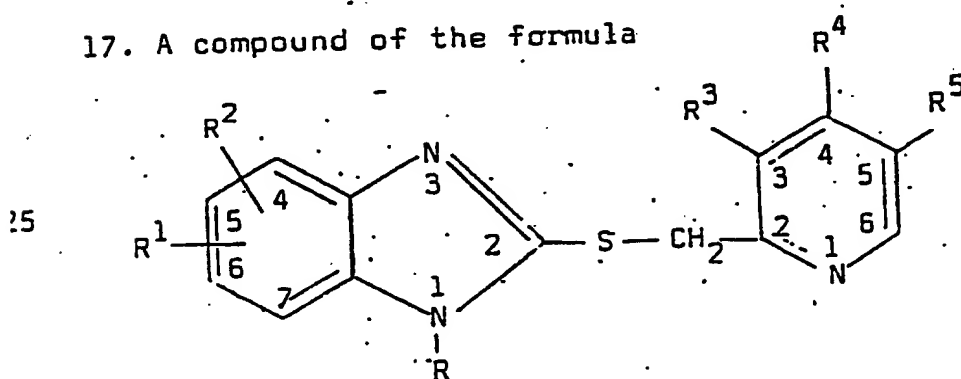
or a therapeutically acceptable salt thereof.

15. A compound as defined in any of claims 1-14, or a therapeutically acceptable salt thereof, for use in inhibiting gastric acid secretion in mammals and man.

16. A compound as defined in any of claims 1-14, or a therapeutically acceptable salt thereof, for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

0

17. A compound of the formula



30 and therapeutically acceptable salts thereof, in which formula

35  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , alkyl containing 1-7 carbon atoms, halogen, alkoxy containing 1-5 carbon atoms, and alkanoyl containing 1-4 carbon atoms;

R is selected from the group consisting of H; alkanoyl containing 1-4 carbon atoms, and carboalkoxy containing 2-6 carbon atoms;

5 and  $R^3$ ,  $R^4$  and  $R^5$ , which are the same or different, are each selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; provided that

10 a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

15 b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; and provided that

20 c) the radicals R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are selected so that the following compounds are excluded:

| R    | $R^1$               | $R^2$             | $R^3$           | $R^4$           | $R^5$           |
|------|---------------------|-------------------|-----------------|-----------------|-----------------|
| H    | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H               | CH <sub>3</sub> | CH <sub>3</sub> |
| H    | 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | CH <sub>3</sub> | H               | CH <sub>3</sub> |
| 25 H | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> |

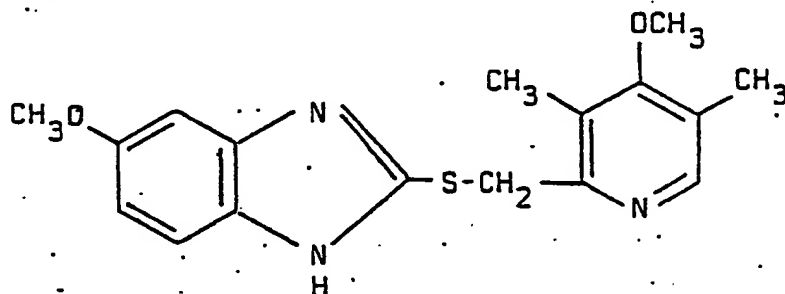
18. A compound according to claim 17 or a therapeutically acceptable salt thereof, wherein R is H,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are as defined in claim 17; and wherein  $R^4$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , or  $OCH_2CH_2OCH_2CH_3$ .

19. A compound according to claim 17, and therapeutically acceptable salts thereof, wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are combined as follows:

| 5  | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |
|----|----------------------|-------------------|---|-----------------|------------------|-----------------|
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 10 | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 15 | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

20. A compound of the formula

20



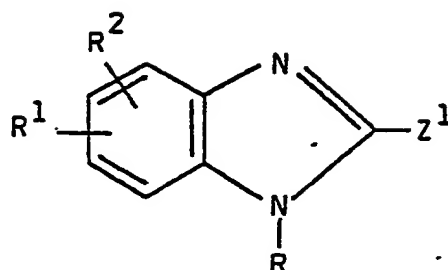
25

or a therapeutically acceptable salt thereof.

21. A process for the preparation of a compound according to any of claims 17-20, by

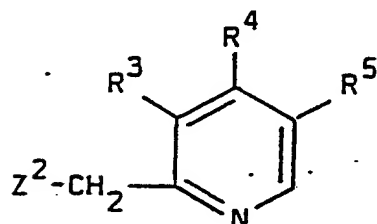
30

A. reacting a compound of the formula



II

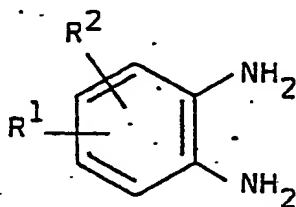
with a compound of the formula



III

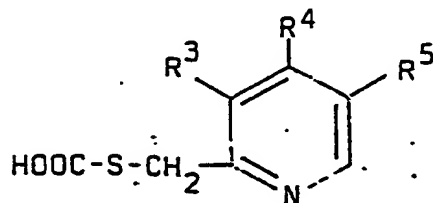
in which formula R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined previously and wherein one of Z<sup>1</sup> and Z<sup>2</sup> is SH and the other of Z<sup>1</sup> and Z<sup>2</sup> is a leaving group;

B. for the preparation of a compound of the formula I wherein R is H, reacting a compound of the formula



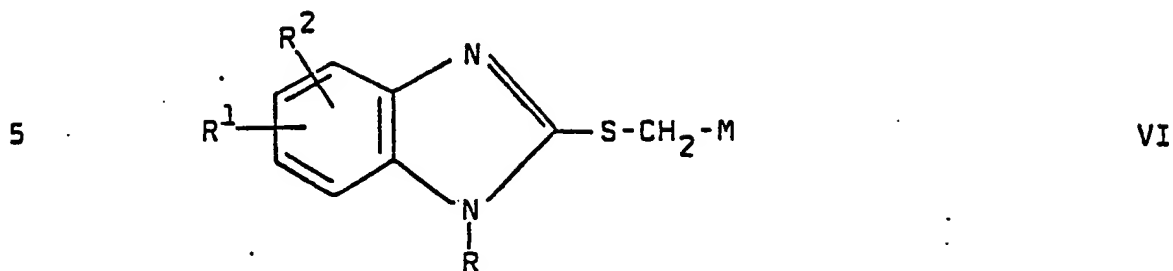
IV

wherein R<sup>1</sup> and R<sup>2</sup> have the same meaning as given above, with a compound of the formula

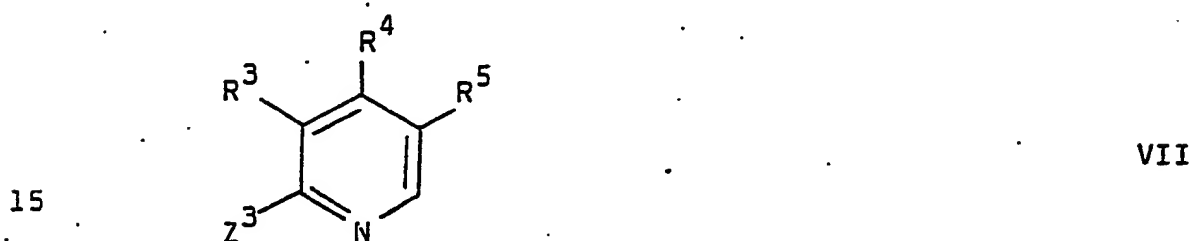


wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

C. reacting a compound of the formula

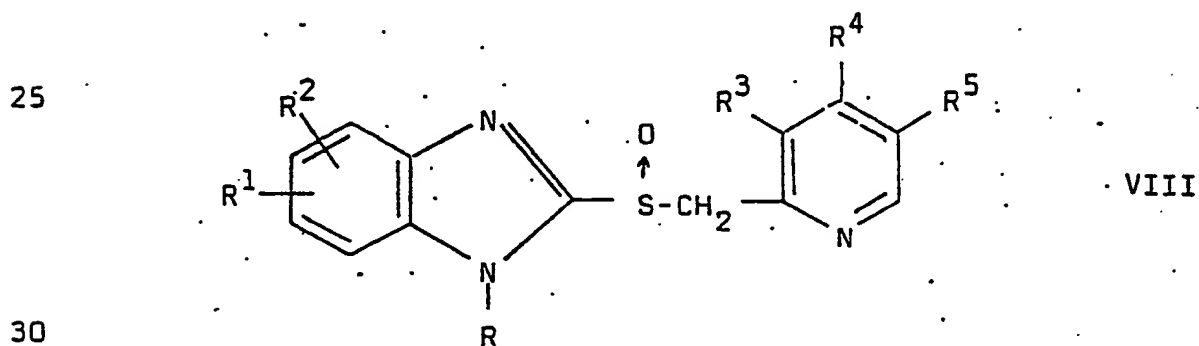


wherein R, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and M is  
 10 K, Na or Li, with a compound of formula



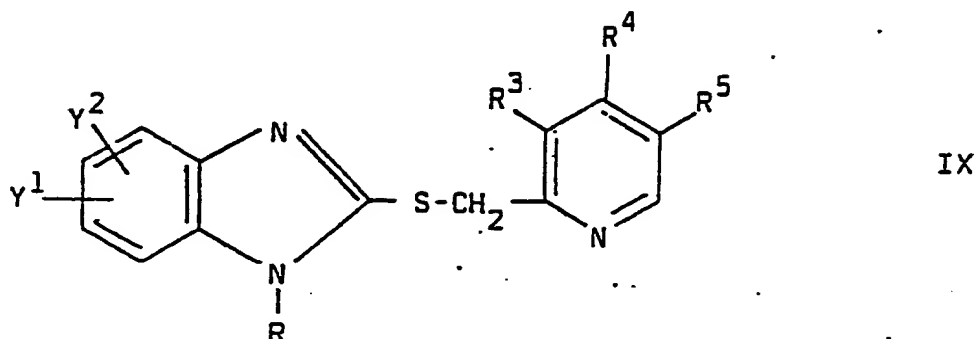
wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meaning given above and Z<sup>3</sup>  
 is a reactive esterified hydroxy group, to the formation of  
 20 a compound of the formula I;

D. reduction of a compound of the formula

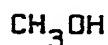


to the formation of a compound of the formula I;

E. for the preparation of a compound of the formula I wherein the radicals  $R^1$  and/or  $R^2$  is  $\text{COOCH}_3$  or  $\text{COOC}_2\text{H}_5$ , reacting a compound of the formula

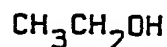


wherein  $R$ ,  $R^3$ ,  $R^4$  or  $R^5$  are as defined above and wherein  $Y^1$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, and  $Y^2$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, or  $R^1$ , with



X

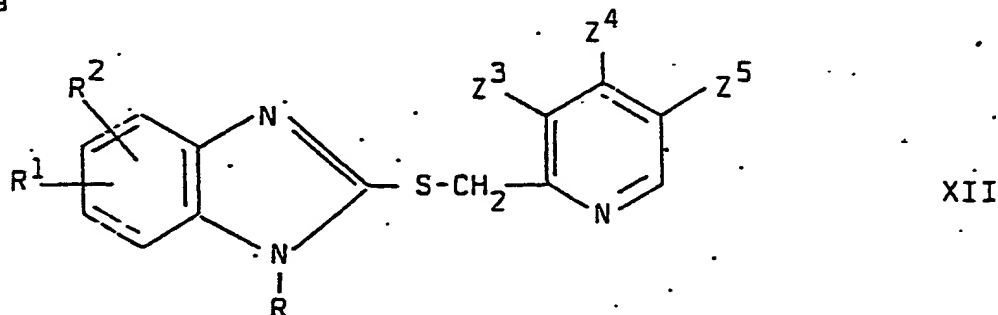
20 or



XI

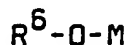
or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein  $R^1$  and/or  $R^2$  is  $\text{CH}_3\text{COO}$  or  $\text{CH}_3\text{CH}_2\text{COO}$ ;

F. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{CH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , reacting a compound of the formula





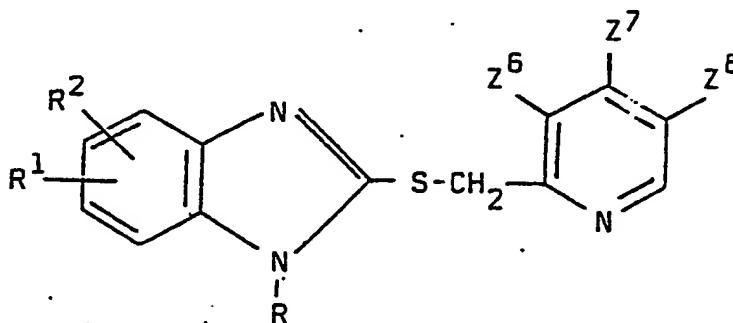
wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above and  $Z^3$ ,  $Z^4$  and  $Z^5$  represent either  $R^3$ ,  $R^4$  and  $R^5$  respectively, or halogen such as Cl, Br, F or I, or  $NO_2$ , whereby at least one of  $Z^3$ ,  $Z^4$  and  $Z^5$  represents halogen or  $NO_2$ , with a compound of the formula



XIII

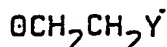
wherein  $R^6$  is  $CH_3$ ,  $C_2H_5$ ,  $CH_2CH_2OCH_3$  or  $CH_2CH_2OCH_2CH_3$ , and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ ;

G. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ , reacting a compound of the formula



XIV

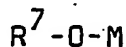
wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above, and  $Z^6$ ,  $Z^7$  and  $Z^8$  represent either  $R^3$ ,  $R^4$  and  $R^5$ , respectively, or a radical



XV

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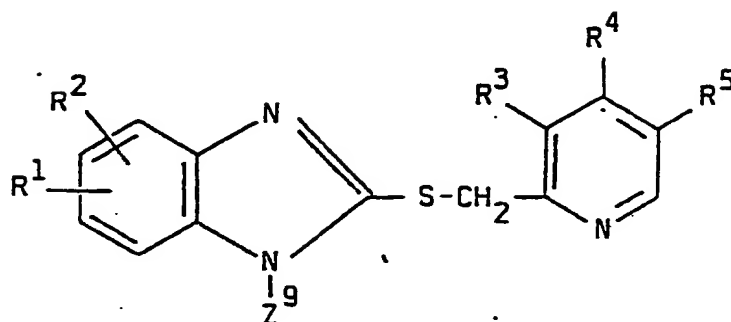
where Y is halogen, whereby at least one of  $Z^6$ ,  $Z^7$  and  $Z^8$  represents  $OCH_2CH_2Y$ , with a compound of the formula



XVI

wherein  $R^7$  is  $CH_3$  or  $CH_2CH_3$  and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ ;

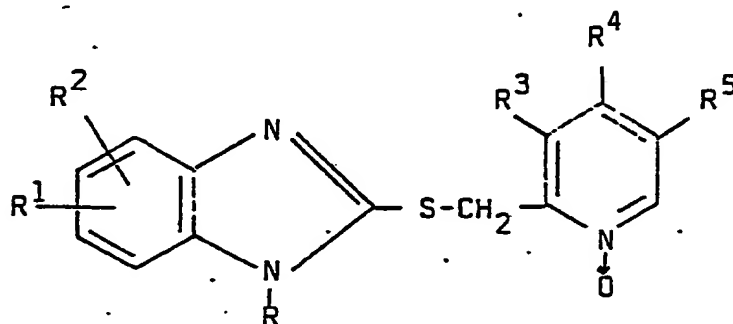
H. for the preparation of a compound of the formula I wherein R is H, hydrolyzing a compound of the formula



XVII

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $Z^9$  is an alkanoyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein R is H;

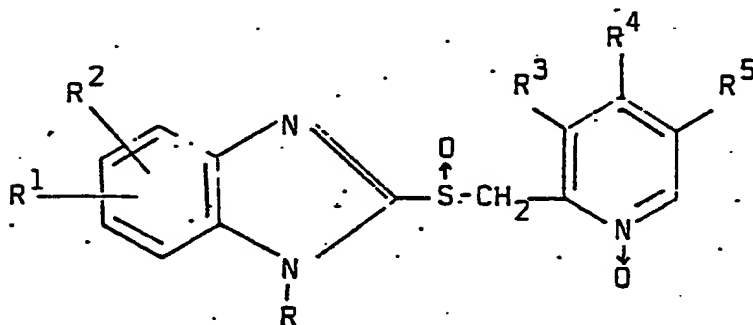
I. reduction of a compound of the formula



XVIII

to the formation of a compound of the formula I;

J. reduction of a compound of the formula



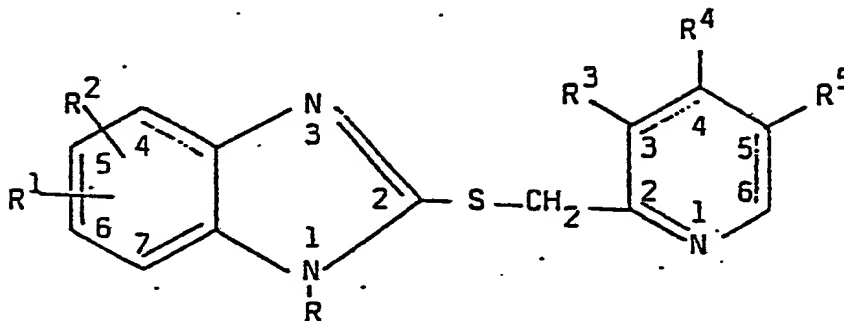
XIX

to the formation of a compound of the formula I;

whereafter, if desired, the compound thus obtained is converted to a therapeutically acceptable salt.

Claims for Austria

1. A process for the preparation of a compound of the formula



and therapeutically acceptable salts thereof, in which formula

$R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , alkyl containing 1-7 carbon atoms, halogen, alkoxy containing 1-5 carbon atoms, and alkanoyl containing 1-4 carbon atoms;

$R$  is selected from the group consisting of H, alkanoyl containing 1-4 carbon atoms, and carboalkoxy containing 2-6 carbon atoms;

and  $R^3$ ,  $R^4$  and  $R^5$ , which are the same or different, are each selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; provided that

a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

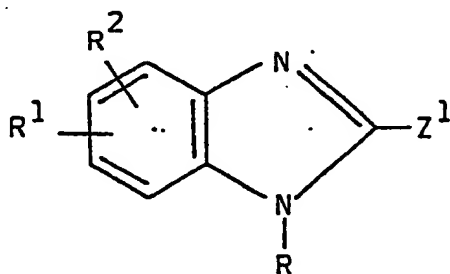
b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; and provided that

c) the radicals  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are selected so that the following compounds are excluded:

| $R$ | $R^1$               | $R^2$             | $R^3$           | $R^4$           | $R^5$           |
|-----|---------------------|-------------------|-----------------|-----------------|-----------------|
| H   | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H               | CH <sub>3</sub> | CH <sub>3</sub> |
| H   | 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | CH <sub>3</sub> | H               | CH <sub>3</sub> |
| H   | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> |

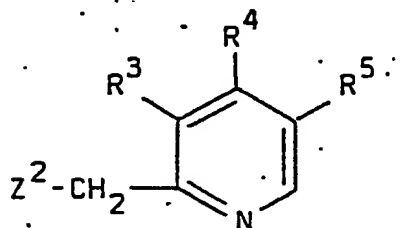
by

A. reacting a compound of the formula



II

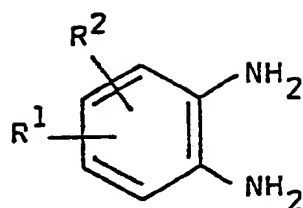
with a compound of the formula



III

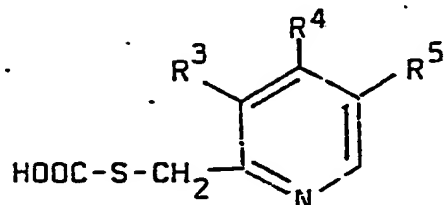
in which formula  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined previously and wherein one of  $Z^1$  and  $Z^2$  is SH and the other of  $Z^1$  and  $Z^2$  is a leaving group;

B. for the preparation of a compound of the formula I wherein  $R$  is H, reacting a compound of the formula



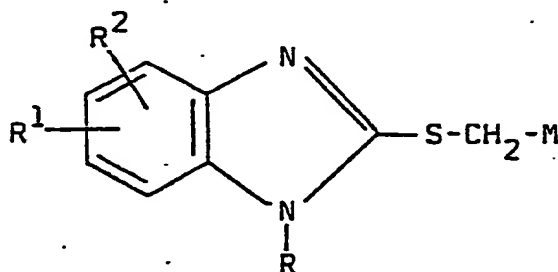
IV

wherein  $R^1$  and  $R^2$  have the same meaning as given above, with a compound of the formula



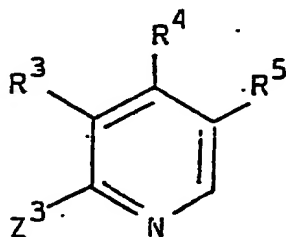
wherein  $R^3$ ,  $R^4$  and  $R^5$  have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

C. reacting a compound of the formula



VI

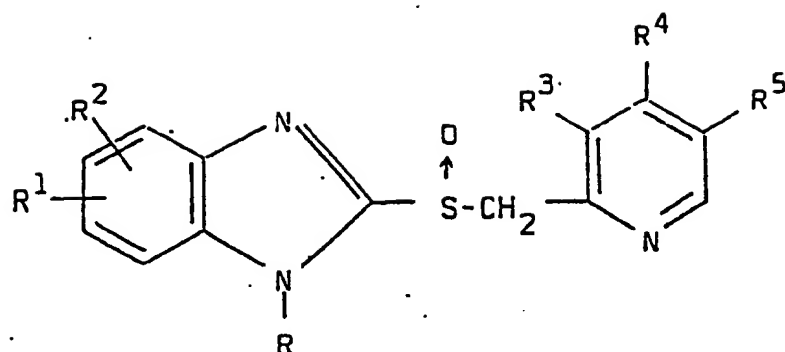
wherein R,  $R^1$  and  $R^2$  have the meaning given above and M is K, Na or Li, with a compound of formula



VII

wherein  $R^3$ ,  $R^4$  and  $R^5$  have the meaning given above and  $Z^3$  is a reactive esterified hydroxy group, to the formation of a compound of the formula I;

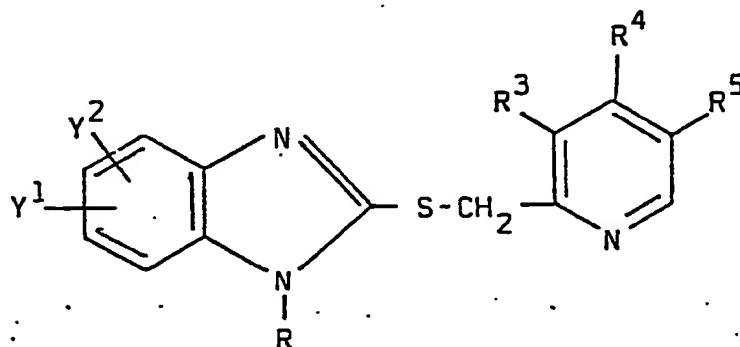
D. reduction of a compound of the formula



VIII

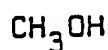
10 to the formation of a compound of the formula I;

E. for the preparation of a compound of the formula I wherein the radicals  $R^1$  and/or  $R^2$  is  $COOCH_3$  or  $COOC_2H_5$ , reacting a compound of the formula



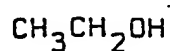
IX

25 wherein  $R$ ,  $R^3$ ,  $R^4$  or  $R^5$  are as defined above and wherein  $Y^1$  is  $-COOH$ , or a functionally equivalent derivative thereof, and  $Y^2$  is  $-COOH$ , or a functionally equivalent derivative thereof, or  $R^1$ , with



X

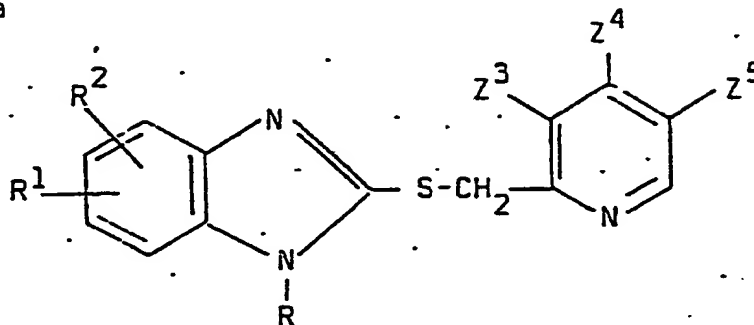
or



XI

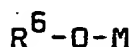
35 or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein  $R^1$  and/or  $R^2$  is  $CH_3COO$  or  $CH_3CH_2COO$ ;

F. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2CH_3$  or  $OCH_2CH_2OCH_2CH_3$ , reacting a compound of the formula



XII

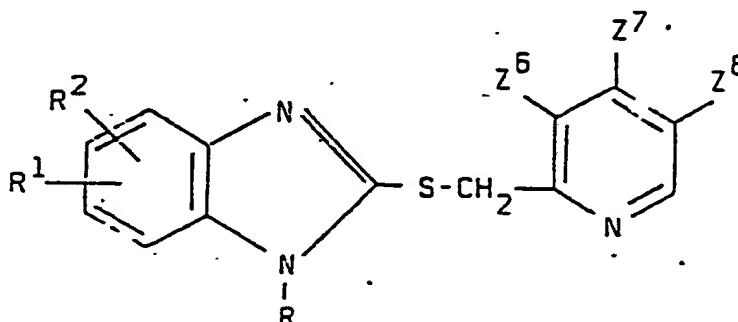
wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above and  $Z^3$ ,  $Z^4$  and  $Z^5$  represent either  $R^3$ ,  $R^4$  and  $R^5$  respectively, or halogen such as Cl, Br, F or I, or  $NO_2$ , whereby at least one of  $Z^3$ ,  $Z^4$  and  $Z^5$  represents halogen or  $NO_2$ , with a compound of the formula



XIII

wherein  $R^6$  is  $CH_3$ ,  $C_2H_5$ ,  $CH_2CH_2OCH_3$  or  $CH_2CH_2OCH_2CH_3$ , and  $M$  is Na, K or Li, to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ ;

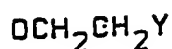
G. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ , reacting a compound of the formula



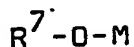
XIV



wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above, and  $Z^6$ ,  $Z^7$  and  $Z^8$  represent either  $R^3$ ,  $R^4$  and  $R^5$ , respectively, or a radical

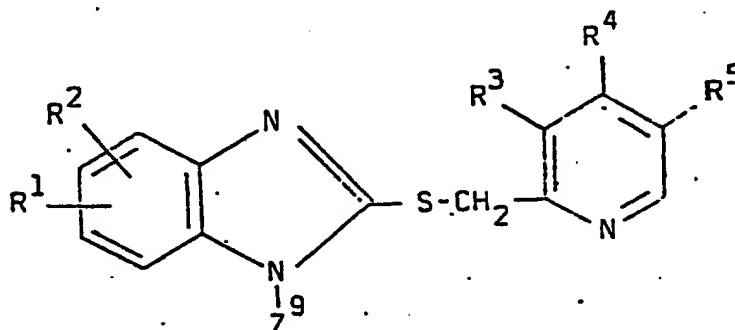


where  $Y$  is halogen, whereby at least one of  $Z^6$ ,  $Z^7$  and  $Z^8$  represents  $OCH_2CH_2Y$ , with a compound of the formula



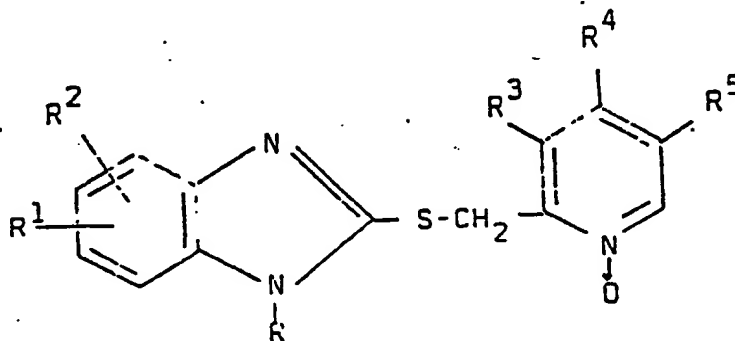
wherein  $R^7$  is  $CH_3$  or  $CH_2CH_3$  and  $M$  is  $Na$ ,  $K$  or  $Li$ , to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ ;

H. for the preparation of a compound of the formula I wherein  $R$  is  $H$ , hydrolyzing a compound of the formula



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $Z^9$  is an alkanoyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein  $R$  is  $H$ ;

I. reduction of a compound of the formula

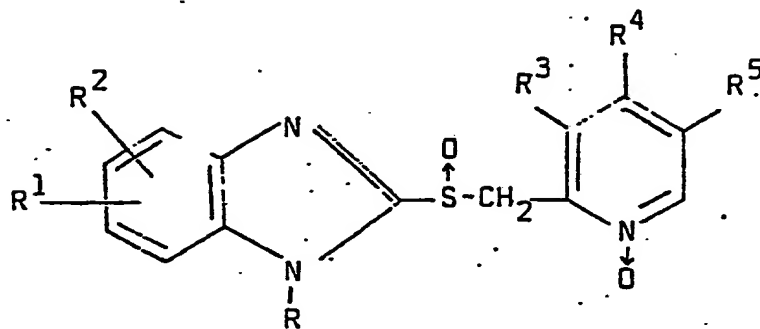


to the formation of a compound of the formula I;

3. reduction of a compound of the formula

5

10



XIX

to the formation of a compound of the formula I;

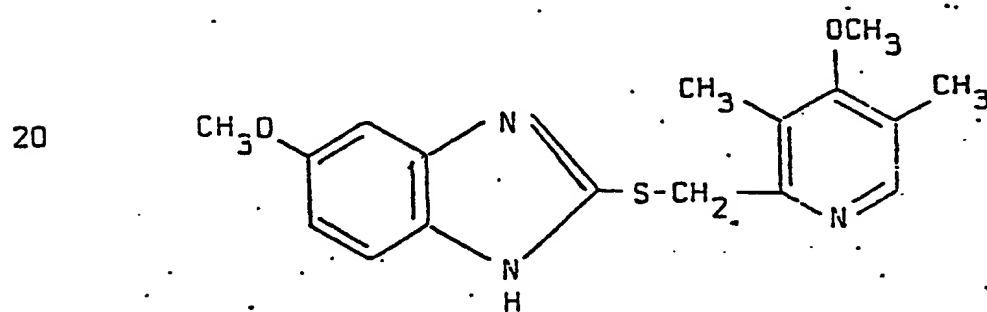
15 whereafter, if desired, the compound of the formula I thus obtained is converted to a therapeutically acceptable salt.

20 2. A process according to claim 1 for the preparation of a compound as defined in claim 1, or a therapeutically acceptable salt thereof, wherein R is H;  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are as defined in claim 1; and wherein  $R^4$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ .

25 3. A process according to claim 1 for the preparation of a compound as defined in claim 1, or a therapeutically acceptable salt thereof, wherein R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are combined as follows:

|    | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |
|----|----------------------|-------------------|---|-----------------|------------------|-----------------|
| 5  | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 10 | 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

- 15 A process according to claim 1 for the preparation of the compound of the formula



- 25 or a therapeutically acceptable salt thereof.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0074341

Application number

EP 82 85 0166

| DOCUMENTS CONSIDERED TO BE RELEVANT   |   |   |  |
|---|---|---|--|
| Category  | Citation of document with indication, where appropriate, of relevant passages   | Relevant to claim   | CLASSIFICATION OF THE APPLICATION (Int. Cl. 7) |
| D,X   | ---<br>EP-A-0 005 129 (HÄSSLE)<br>*Page 2,3,5 to 7,9 to 11,13,14;<br>examples 31,33-34; claims 15,16*   | 17-21   | C 07 D 401/12<br>A 61 K 31/415<br>A 61 K 31/44 |
| A   | ---<br>FR-A-2 392 021 (HÄSSLE)<br>*Pages 1,4 to 6,11 to 13; exam-<br>ples 31,33-37,39-41*& US - A - 4<br>045 563 & NL - A - 7 513 141 & CH<br>- A - 623 582 & AT - B - 351 524<br>& AT - B - 337 697 & BE - A - 834<br>973 & SE - A - 416 649 | 17-21   |  |
| A   | ---<br>FR-A-2 261 007 (HÄSSLE)<br>-----   |   |  |
| The present search report has been drawn up for all claims  |   |   | TECHNICAL FIELDS<br>SEARCHED (Int. Cl. 7)      |
|   |   |   | C 07 D 401/00<br>A 61 K 31/00                  |
| Place of search<br>THE HAGUE  |   | Date of completion of the search<br>18-11-1982  | Examiner<br>DE BUYSER I.A.F.                   |
| <b>CATEGORY OF CITED DOCUMENTS</b>  |   |   |  |
| X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document |   | T : the theory or principle underlying the invention<br>E : earlier patent document, but published later, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>& : member of the same patent family, corresponding document |  |



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73 Proprietor: Aktiebolaget Hässle  
Kärragatan 5  
S-431 83 Mölndal (SE)

72 Inventor: Carlsson, Enar Ingemar  
Ingegårdsvägen 2C  
S-421 68 Frölunda (SE)  
Inventor: Junggren, Ulf Krister  
Dammvägen 7  
S-43500 Mölnlycke (SE)  
Inventor: Larsson, Hakan Sigurd  
Hagalundsvägen 4  
S-430 65 Rävlanda (SE)  
Inventor: von Wittken Sundell, Gunhild Wika  
Solliden 2  
S-436 00 Askim (SE)

74 Representative: Wurm, Bengt Runio et al  
Patent and Trade Mark Department AB ASTRA  
S-151 85 Södertälje (SE)

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## Description

## Field of the invention

The object of the present invention is to provide compounds which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the treatment of peptic ulcer.

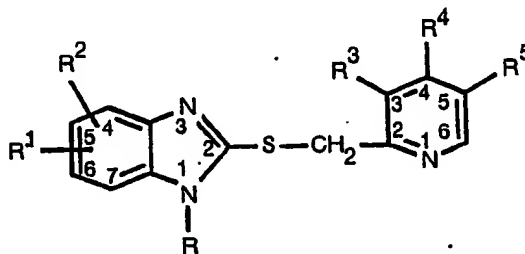
The present invention relates to the use of a group of benzimidazole derivatives, or therapeutically acceptable salts thereof, for inhibiting gastric acid secretion in mammals and man. In a more general sense, the invention relates to the use of the compounds for treatment of gastrointestinal inflammatory diseases in mammals and man, including i.e. gastric and duodenal ulcer. Furthermore, it relates to the use of these compounds for treatment of other gastrointestinal disorders, where a gastric antisecretory effect is desirable i.e. in patients with gastrinomas and in patients with acute upper gastrointestinal bleeding. The invention also relates to pharmaceutical compositions containing at least one member of the said group of benzimidazole derivatives, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to new compounds, and therapeutically acceptable salts thereof, within the said group of benzimidazole derivatives, and to processes for preparation of such new compounds.

## Prior art

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the British patent specifications 1 500 043 and 1 525 958, in the US patent 4 182 766 and in the European patent specification No. 0 005 129.

## The invention

It has been found that the compounds of the formula



and therapeutically acceptable salts thereof in which formula

R<sup>1</sup> and R<sup>2</sup> are the same or different and each selected from the group consisting of H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, alkyl containing 1—7 carbon atoms, halogen, alkoxy containing 1—5 carbon atoms, and alkanoyl containing 1—4 carbon atoms;

R is selected from the group consisting of H, alkanoyl containing 1—4 carbon atoms, and carbealkoxy containing 2—6 carbon atoms; and

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, which are the same or different, are each selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, provided that

a) at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is selected from the group consisting of CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and

b) when two of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are H, then the remaining radical R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is selected from the group consisting of OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

c) when R is H, R<sup>1</sup> or R<sup>2</sup> is CF<sub>3</sub> and R<sup>3</sup> and R<sup>5</sup> are CH<sub>3</sub> and/or H, R<sup>4</sup> is not OCH<sub>3</sub>;

are effective as inhibitors of gastric acid secretion in mammals and man. The compounds of the formula I, and therapeutically acceptable salts thereof, are stable in gastric juice, which is of importance at oral administration.

Illustrative examples of the radicals in the formula I are:

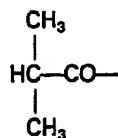
Alkyl groups R<sup>1</sup> and R<sup>2</sup>: methyl, ethyl, n-propyl, i-propyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl, n-pentyl, n-hexyl, n-heptyl. It is preferred that alkyl groups R<sup>1</sup> and R<sup>2</sup> contains 1, 2, 3 or 4 carbon atoms. The preferred alkyl group is methyl.

Halogen R<sup>1</sup> and R<sup>2</sup>: chloro, bromo, fluoro, iodo. The preferred halogen groups are chloro and bromo.

Alkoxy groups R<sup>1</sup> and R<sup>2</sup>: methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec.-butoxy, isobutoxy, tert.-butoxy, n-pentoxy. It is preferred that alkoxy groups R<sup>1</sup> and R<sup>2</sup> contain 1, 2 or 3 carbon atoms. The preferred alkoxy group is methoxy.

Alkanoyl groups R, R<sup>1</sup> and R<sup>2</sup>: HCO—, CH<sub>3</sub>CO—, CH<sub>3</sub>CH<sub>2</sub>CO—, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CO—,

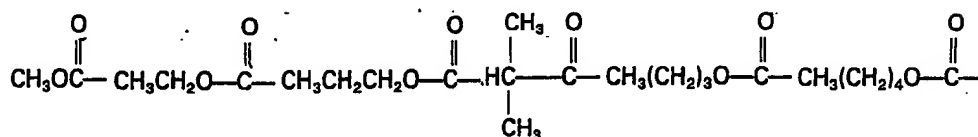
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The preferred alkanoyl group R<sup>1</sup> and R<sup>2</sup> is CH<sub>3</sub>CO. The preferred alkanoyl group R is CH<sub>3</sub>CO.  
Carboalkoxy groups R:

15



It is preferred that carboalkoxy groups R contains 2 or 3 carbon atoms. Thus, the groups CH<sub>3</sub>OCO— and CH<sub>3</sub>CH<sub>2</sub>OCO— are preferred.

20

The preferred meaning of the radical R is H.

Preferred combinations of the radicals in the formula I, subject to the two provisos a) and b) given above, are given in Table 1 below.

TABLE 1

25

Preferred embodiments of R<sup>1</sup>, R<sup>2</sup>, R, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>

| 30 | R <sup>1</sup> and R <sup>2</sup> ,<br>the same or different if<br>not indicated otherwise        | R | R <sup>3</sup> , R <sup>4</sup> and R <sup>5</sup> ,<br>the same or different if<br>not indicated otherwise  |
|----|---|---|--|
| 35 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, halogen, alkoxy,<br>alkanoyl | H | H, CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> , OCH <sub>3</sub> ,<br>OC <sub>2</sub> H <sub>5</sub> , OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> |
| 40 | H, COOCH <sub>3</sub> , CH <sub>3</sub> , Cl, Br,<br>OCH <sub>3</sub> , CH <sub>3</sub> CO        | H | H, CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> , OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>   |
| 45 | H, COOCH <sub>3</sub> , alkyl<br>alkoxy, alkanoyl   | H | H, CH <sub>3</sub> , OCH <sub>3</sub> , OC <sub>2</sub> H <sub>5</sub>   |
| 50 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, halogen, alkoxy,<br>alkanoyl | H | R <sup>3</sup> : CH <sub>3</sub><br>R <sup>4</sup> : OCH <sub>3</sub><br>R <sup>5</sup> : CH <sub>3</sub>  |
| 55 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl          | H | R <sup>3</sup> : H<br>R <sup>4</sup> : OCH <sub>3</sub>  |
| 60 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl          | H | R <sup>3</sup> : CH <sub>3</sub><br>R <sup>4</sup> : OCH <sub>3</sub><br>R <sup>5</sup> : H  |
| 65 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl          | H | R <sup>3</sup> : H<br>R <sup>4</sup> : OCH <sub>3</sub><br>R <sup>5</sup> : H  |
|    | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl          | H | R <sup>3</sup> : CH <sub>3</sub><br>R <sup>4</sup> : H<br>R <sup>5</sup> : CH <sub>3</sub>   |

TABLE 1 (cont.)

| 5  | R <sup>1</sup> and R <sup>2</sup> ,<br>th same or different if<br>not indicated otherwise | R  | R <sup>3</sup> , R <sup>4</sup> and R <sup>5</sup> ,<br>the same or different if<br>not indicated otherwise  |
|----|---|----|--|
| 10 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy,<br>alkanoyl  | H. | R <sup>3</sup> : H<br>R <sup>4</sup> : OCH <sub>3</sub> , OC <sub>2</sub> H <sub>5</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ,<br>OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub><br>R <sup>5</sup> : H |
| 15 | H, COOCH <sub>3</sub> , COOC <sub>2</sub> H <sub>5</sub> ,<br>alkyl, alkoxy<br>alkanoyl   | H  | R <sup>3</sup> : CH <sub>3</sub><br>R <sup>4</sup> : CH <sub>3</sub><br>R <sup>5</sup> : CH <sub>3</sub>   |

The radicals R<sup>1</sup> and R<sup>2</sup> can be bound to the benzimidazole nucleus in any of the positions 4, 5, 6 and 7 as depicted in formula I. It is preferred that R<sup>1</sup> and R<sup>2</sup> are in position 5 and/or 6.

Preferred individual compounds among those included in the formula I are given in the following Table 2:

TABLE 2

| 25 | Preferred individual compounds |                   |   |                 |                  |                 |
|----|--------------------------------|-------------------|---|-----------------|------------------|-----------------|
|    | R <sup>1</sup>                 | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |
| 30 | 5-OCH <sub>3</sub>             | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub>           | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub>           | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 35 | 5-COCH <sub>3</sub>            | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>            | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 40 | 5-CH <sub>3</sub>              | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>            | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5-OCH <sub>3</sub>             | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 45 | 5-COCH <sub>3</sub>            | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub>           | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
|    | 5-COCH <sub>3</sub>            | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 50 | 5-COOCH <sub>3</sub>           | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

Further preferred individual compounds are those exemplified in the examples given elsewhere in this specification.

In the prior art cited above, no medicinal use is disclosed for the compounds of the formula I. Thus, the present invention comprises pharmaceutical compositions containing a compound of the formula I or a therapeutically acceptable salt thereof as active ingredient, for inhibiting gastric acid secretion in mammals and man.

The compounds of the formula I where in R<sup>1</sup> and R<sup>2</sup> are as defined above except CF<sub>3</sub> and NO<sub>2</sub>, R is H and R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are H, CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> are generically disclosed as chemical intermediates in the European patent No. 0 005 129. The specific compounds disclosed in the following Table 3 are disclosed in the said European patent No. 0 005 129.



TABLE 3

Compounds disclosed in European patent no. 0 005 129.

| R | R <sup>1</sup>      | R <sup>2</sup>    | R <sup>3</sup>  | R <sup>4</sup>  | R <sup>5</sup>  | Remark        |
|---|---------------------|-------------------|-----------------|-----------------|-----------------|---------------|
| H | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H               | CH <sub>3</sub> | CH <sub>3</sub> | base          |
| H | 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | CH <sub>3</sub> | H               | CH <sub>3</sub> | hydrochloride |
| H | 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | base          |

The present invention, in so far as it concerned compounds of the formula I subject to the above provisos by themselves, their pharmaceutically acceptable salts, and processes for their preparations, relates to

- i) the compounds of the formula I wherein R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is C<sub>2</sub>H<sub>5</sub>
- ii) the compounds of the formula I wherein R is alkanoyl or carboalkoxy
- iii) the compounds of the formula I wherein R is H except the compounds wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are combined as follows:

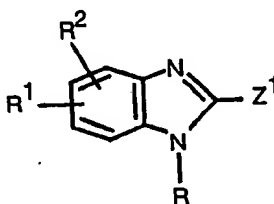
| R <sup>1</sup>      | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>  | R <sup>5</sup>  |
|---------------------|-------------------|---|-----------------|-----------------|-----------------|
| 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub> | CH <sub>3</sub> |
| 4-CH <sub>3</sub>   | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H               | CH <sub>3</sub> |
| 5-COCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> |

iv) the compounds of the formula I wherein R<sup>1</sup> and/or R<sup>2</sup> are CF<sub>3</sub> or NO<sub>2</sub>.

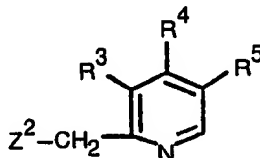
The preferred compounds within the groups i), ii), iii) and iv) will comprise the same compounds that are indicated as preferred in Table 1 and Table 2 above, subject to the proviso that the specific compounds listed in Table 3 are excluded.

The compounds of the formula I can be prepared by known methods such as

A. reacting a compound of the formula



with a compound of the formula



in which formulas R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined previously and wherein one of Z<sup>1</sup> and Z<sup>2</sup> is SH and the other is a leaving group.

Examples of leaving groups Z<sup>1</sup> and Z<sup>2</sup> in the compounds II and III are halogens, preferably chlorine, bromine or iodine, acyl radicals, for example, residues of strong organic sulfonic acids, for instance, of an arylsulfonic acid, for example, tosyloxy, or an alkylsulfonic acid, for example mesyloxy; alkylmercapto groups, for example, methylmercapto; alkylsulfinyl groups, for example, methylsulfinyl and the like.

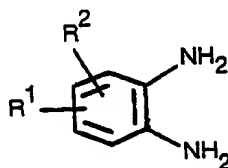
Thus, Z<sup>1</sup> or Z<sup>2</sup> when designating leaving groups may be a reactive esterified hydroxyl group.

The reaction of a compound of formula II above with a compound of formula III is conveniently carried out in the presence of a suitable solvent that is inert under the reaction conditions utilized as described hereinafter. The reaction may further be carried out in the presence of a suitable base. Suitable bases include, for example, inorganic bases such as sodium or potassium hydroxide, sodium or potassium hydride and the like, organic bases such as tertiary amines, for example, triethylamine and the like.

Suitable solvents for the above described reaction include, for example, alcohols, preferably lower alkanols such as, methanol and ethanol; mixtures of such alcohols with water, ethers, such as, tetrahydrofuran; halogenated hydrocarbons, such as, methylene chloride and chloroform, and the like.

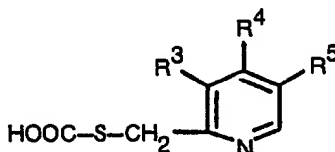
The reaction of the compounds of formulas II and III may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture. It is preferred to carry out the reaction, however, at a temperature at or close to the boiling point of the reaction mixture for the preparation of a compound of the formula I wherein R is H;

B. reacting a compound of the formula



IV

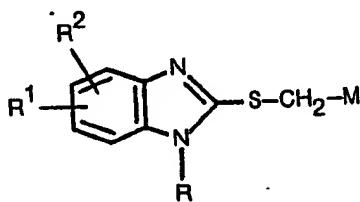
wherein R<sup>1</sup> and R<sup>2</sup> have the same meaning as given above with a compound of the formula



V

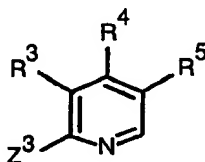
wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

C. reacting a compound of the formula



VI

wherein R, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and M is K, Na, or Li, with a compound of formula

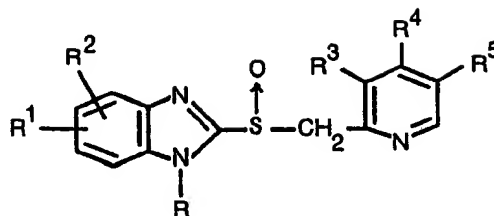


VII

wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meaning given above and Z<sup>3</sup> is a reactive esterified hydroxy group, to the formation of a compound of the formula I.

The reactive esterified hydroxy group Z<sup>3</sup> may, as in the case of Z<sup>1</sup> and Z<sup>2</sup>, be a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, or esterified with sulfuric acid or with a strong organic sulfonic acid such as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

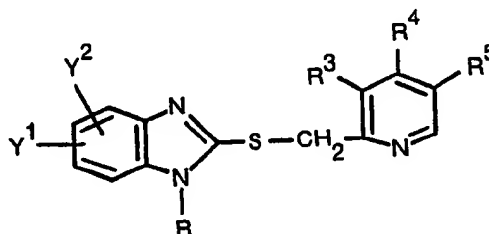
D. reduction of a compound of the formula



VIII

to the formation of a compound of the formula I:

E. for the preparation of a compound of the formula I wherein the radicals of R<sup>1</sup> and/or R<sup>2</sup> is COOCH<sub>3</sub> or COOC<sub>2</sub>H<sub>5</sub>, reacting a compound of the formula



IX

wherein R, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> are as defined above and wherein Y<sup>1</sup> is —COOH, or a functionally equivalent derivative thereof, and Y<sup>2</sup> is —COOH, or a functionally equivalent derivative thereof, or R<sup>1</sup>, with



X

or



XI

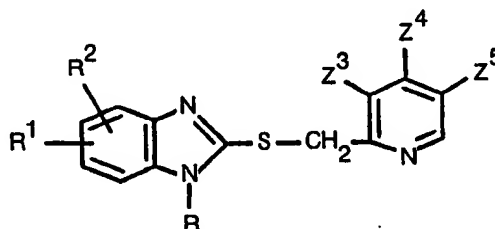
or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein R<sup>1</sup> and/or R<sup>2</sup> is CH<sub>3</sub>COO or CH<sub>3</sub>CH<sub>2</sub>COO.

This reaction is an ordinary esterification which is carried out in customary manner.

Functionally equivalent derivatives of the hydroxy group in the compounds X and XI are for example halogen such as Cl or Br, or —N<sub>2</sub>.

Functionally equivalent derivatives of the carboxyl group Y<sup>1</sup> and Y<sup>2</sup> are for example a metal carboxylate group or an activated carboxyl group, in which case the radicals Y<sup>1</sup> or Y<sup>2</sup> are for example an acid chloride, an alkyl ester, an acid anhydride or a mixed anhydride with formic esters or carboxylic acids, sulphonic or inorganic esters or derivatives obtained by a reaction between a carboxylic acid and a carbodiimide or similarly functioning compounds such as N<sup>1</sup>N<sup>1</sup>-carbonyldiimidazole or N-ethyl-5-phenylisoxazolium-3<sup>1</sup>-sulphonate, the derivative of the carboxyl group Y<sup>1</sup> or Y<sup>2</sup> being a metal carboxylate group when the hydroxyl group in the compounds X or XI is replaced with halogen. A further functionally equivalent derivative of the carboxyl groups Y<sup>1</sup> and Y<sup>2</sup> is the group —CN, in which case a cyanide is reacted with a compound of the formula X or XI with subsequent hydrolysis to give a compound of the formula I wherein R<sup>1</sup> and/or R<sup>2</sup> is CH<sub>3</sub>COO or CH<sub>3</sub>CH<sub>2</sub>COO.

F. for the preparation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, reacting a compound of the formula



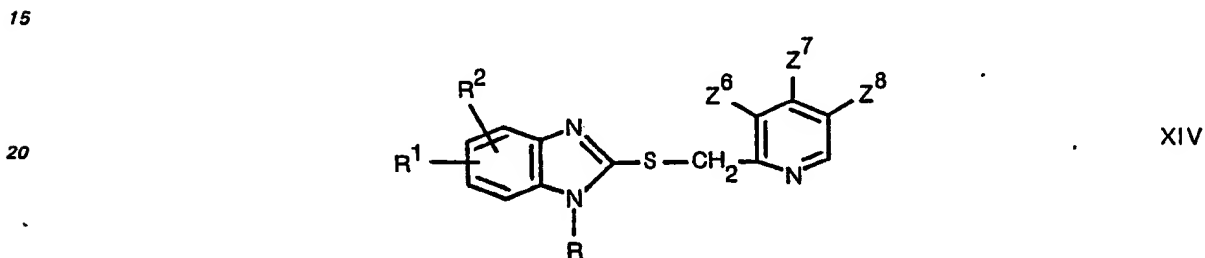
XII

wherein R, R<sup>1</sup> and R<sup>2</sup> are as defined above and Z<sup>3</sup>, Z<sup>4</sup> and Z<sup>5</sup> represent either R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, respectively, or halogen such as Cl, Br, F or I, or NO<sub>2</sub>, where by at least one of Z<sup>3</sup>, Z<sup>4</sup> and Z<sup>5</sup> represents halogen or NO<sub>2</sub>, with a compound of the formula



wherein R<sup>6</sup> is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and M is Na, K, or Li, to the formation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

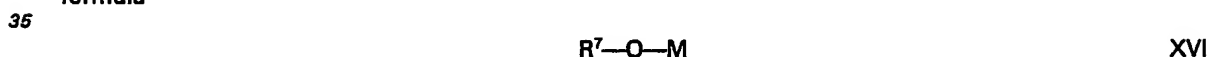
10 G. for the preparation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, reacting a compound of the formula



wherein R, R<sup>1</sup> and R<sup>2</sup> are as defined above, and Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represent either R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, respectively, or a radical



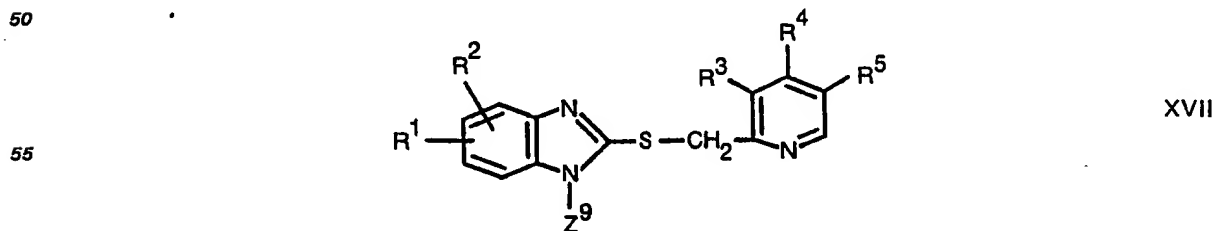
where Y is halogen, whereby at least one of Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represent OCH<sub>2</sub>CH<sub>2</sub>Y, with a compound of the formula



wherein R<sup>7</sup> is CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub> and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>.

40 Method F and Method G represent the known Williamson ether synthesis and is carried out in known manner.

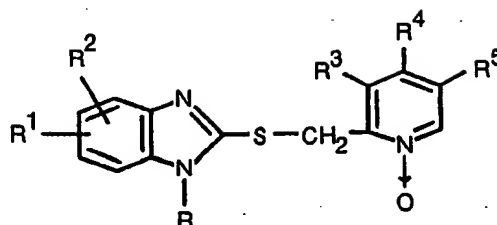
45 H. for the preparation of a compound of the formula I wherein R is H, hydrolyzing a compound of the formula



60 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above and Z<sup>9</sup> is an alkanoyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein R is H.

65 The radical Z<sup>9</sup> can be an alkanoyl group containing 1—6 carbon atoms or a carboalkoxy group containing 2—6 carbon atoms.

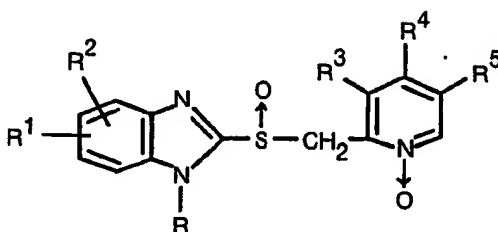
## I. reduction of a compound of the formula



XVIII

to the formation of a compound of the formula I.

## J. reduction of a compound of the formula



XIX

to the formation of a compound of the formula I.

Depending on the process conditions and the starting materials, the end product of the formula I is obtained either as the free base or as a salt. Both the free base and the salts of the end products are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. Acid addition salts of the new compounds may in a manner known *per se* be transformed into free base using basic agents such as alkali or by ion exchange. The free bases obtained may also form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfonic acid, phosphoric acid, nitric acid, and perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, salicylic acid or p-aminosalicylic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid, naphthylsulfonic acid or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered in higher purity from a new salt solution.

The starting materials utilized in the processes A—J are known or may, if they should be new, be obtained according to processes known *per se*.

In clinical use the active compounds of the formula I will normally be administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains the active component either in the form of free base or in the form of a pharmaceutically acceptable, non-toxic salt, as described earlier, optionally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. The compounds may also be used without carrier material. Usually the amount of active compound is between 0.1 and 99% by weight of the preparation, for example between 0.5 to 20% by weight in preparations for injection and between 2 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the formula I in the form of dosage units for oral administration, the active compound may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, a starch such as potatoe starch, corn starch, or amylopectin, cellulose derivatives or gelatin, and may also include a lubricant such as magnesium stearate, calcium stearate or polyethyl neglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, a core prepared as described above may be coated with a concentrated sugar solution which may contain gum arabic, gelatin, talc, titanium dioxide or alternatively with a lacquer dissolved in volatile

organic solvents or mixtures of solvents. To this coating various dyes may be added in order to distinguish tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in admixture with a neutral fatty base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in admixture with a vegetable oil or with paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2% to 20% by weight of the active ingredient, the remainder comprising for example sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as sterile solution, for example in pyrogen-free water, of a water soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different dosage unit ampoules.

The dosage at which the active substances are administered may vary within a wide range and will depend on various factors such as for example the individual requirements of each patient and the manner of administration. In general, oral dosages will be in the range from 100 to 400 mg/day of active substance and intravenous dosages in a range from 5 to 20 mg/day.

The invention is illustrated by the following examples.

#### Example 1

Method A. Preparation of 2-[2-(3,5-dimethyl-4-methoxy)pyridyl(methylthio)]-5-COCH<sub>3</sub>-6-CH<sub>3</sub>-benzimidazole

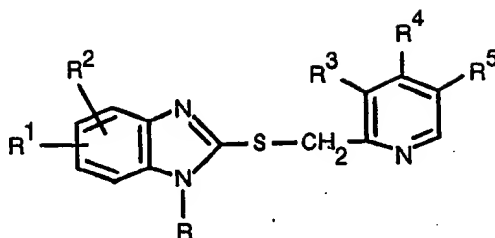
22.2 g (0.1 mole) of 3,5-dimethyl-4-methoxy-2-chloromethylpyridine hydrochloride and 20.6 g (0.1 mole) of 5-COCH<sub>3</sub>-6-CH<sub>3</sub>-2-mercapto benzimidazole was dissolved in 250 ml of methanol whereafter 4 g (0.1 mole) NaOH dissolved in 25 ml H<sub>2</sub>O was added. The mixture was heated to reflux and an additional amount of 4 g (0.1 mole) NaOH in 25 ml H<sub>2</sub>O was added dropwise during 15 min. The mixture was thereafter refluxed during 6 hours whereafter it was cooled and diluted with 500 ml H<sub>2</sub>O. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried and evaporated. The remainder was recrystallized from acetonitrile giving the title substance in the form of free base. Yield: 30 g (85% of the theoretical yield). M.P.: 139°C.

#### Examples 2—50

The compounds identified by example numbers 2—50 in the following Table 4 were prepared using the same method of preparation as in Example 1. The compounds were obtained in the form of their free base. The compound of Example 1 is also included in the table.

TABLE 4

Identifying data for compounds of the invention



| Example no | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>                 | R <sup>5</sup>  | M.p. °C   |
|------------|----------------------|-------------------|---|-----------------|--------------------------------|-----------------|-----------|
| 1          | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>                | CH <sub>3</sub> | 148       |
| 2          | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>                | CH <sub>3</sub> | 125       |
| 3          | 5-COOCH <sub>3</sub> | H                 | H | H               | CH <sub>3</sub>                | CH <sub>3</sub> | 136       |
| 4          | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | H               | 140       |
| 5          | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | H               | 170 (oil) |
| 6          | 4-CH <sub>3</sub>    | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H                              | CH <sub>3</sub> | 206       |
| 7          | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H                              | CH <sub>3</sub> | 125       |
| 8          | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | CH <sub>3</sub> | 100 (oil) |
| 9          | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub>               | H               | 97        |
| 10         | 4-CH <sub>3</sub>    | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub>               | H               | 110       |
| 11         | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 139       |
| 12         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | H                              | CH <sub>3</sub> | 130       |
| 13         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>                | CH <sub>3</sub> | 184       |
| 14         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub>               | H               | 146       |
| 15         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OC <sub>2</sub> H <sub>5</sub> | H               | 90—94     |
| 16         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub>               | H               | 160       |
| 17         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 119       |
| 18         | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub>               | CH <sub>3</sub> | 184       |
| 19         | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | H                              | CH <sub>3</sub> | 130       |
| 20         | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 175       |
| 21         | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 122—124   |
| 22         | 5-OCH <sub>3</sub>   | H                 | H | H               | OCH <sub>3</sub>               | CH <sub>3</sub> | 168       |
| 23         | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 110—119   |
| 24         | 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub>               | CH <sub>3</sub> | 148       |

TABLE 4 (cont.)

| Example<br>no | R <sup>1</sup>                      | R <sup>2</sup>    | R | R <sup>3</sup>   | R <sup>4</sup>                                    | R <sup>5</sup>                | M.p.<br>°C |
|---------------|-------------------------------------|-------------------|---|------------------|---|-------------------------------|------------|
| 25            | H                                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               | 125        |
| 26            | 5-Cl                                | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               | 180        |
| 27            | 3-CH <sub>3</sub>                   | H                 | H | H                | OC <sub>2</sub> H <sub>4</sub> OCH <sub>3</sub> H |                               | 100        |
| 28            | 5-COOC <sub>2</sub> H <sub>5</sub>  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               | 130        |
| 29            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | CH <sub>3</sub>               | 157        |
| 30            | CH <sub>3</sub>                     | CH <sub>3</sub>   | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             | 140        |
| 31            | COOCH <sub>3</sub>                  | CH <sub>3</sub>   | H | CH <sub>3</sub>  | H   | CH <sub>3</sub>               | 125        |
| 32            | 5-C(CH <sub>3</sub> ) <sub>3</sub>  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 33            | 5-NO <sub>2</sub>                   | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 34            | 5-CH <sub>3</sub>                   | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 35            | 4-CH <sub>3</sub>                   | 6-CH <sub>3</sub> | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 36            | 5-C <sub>2</sub> H <sub>5</sub>     | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 38            | 5-CH(CH <sub>3</sub> ) <sub>2</sub> | H                 | H | HCH <sub>3</sub> | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 39            | 5-Cl                                | 6-Cl              | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 40            | 5-OC <sub>2</sub> H <sub>5</sub>    | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 41            | 5-Br                                | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | CH <sub>3</sub>               |            |
| 42            | 5-OCH <sub>3</sub>                  | H                 | H | OCH <sub>3</sub> | H   | H                             |            |
| 43            | 5-Cl                                | H                 | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             |            |
| 44            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             |            |
| 45            | 5-CH <sub>3</sub>                   | 7-CH <sub>3</sub> | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             |            |
| 46            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | OCH <sub>3</sub>                                  | H                             |            |
| 47            | 5-COOCH <sub>3</sub>                | 7-CH <sub>3</sub> | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             |            |
| 48            | 5-COCH <sub>3</sub>                 | H                 | H | CH <sub>3</sub>  | CH <sub>3</sub>                                   | H                             |            |
| 49            | 5-OCH <sub>3</sub>                  | H                 | H | CH <sub>3</sub>  | OC <sub>2</sub> H <sub>5</sub>                    | CH <sub>3</sub>               |            |
| 50            | 5-COOCH <sub>3</sub>                | 6-CH <sub>3</sub> | H | H                | OCH <sub>3</sub>                                  | C <sub>2</sub> H <sub>5</sub> |            |

Identifying data for the compounds according to examples 32—50 are given in the following table 5.



TABLE 5

NMR data for compounds of the invention

| Compound according<br>to example no. | NMR data<br>$\delta$  |
|--------------------------------------|---|
| 32                                   | 1.37 (s, 9H), 2.26 (s, 3H), 2.30 (s, 3H),<br>3.76 (s, 3H), 4.37 (s, 2H), 7.25 (k, 1H),<br>7.49 (d, 1H), 7.57 (d, 1H), 8.30 (s, 1H)                                |
| 33                                   | 2.21 (s, 3H), 2.31 (s, 3H), 3.75 (s, 3H),<br>4.77 (s, 2H), 7.64 (d, 1H), 8.11 (k, 1H),<br>8.23 (s, 1H), 8.36 (d, 1H)  |
| 34                                   | 2.23 (s, 3H), 2.28 (s, 3H), 2.33 (s, 6H),<br>3.75 (s, 3H), 4.33 (s, 2H), 7.29 (s, 2H),<br>8.23 (s, 1H)  |
| 35                                   | 2.28 (s, 3H), 2.33 (s, 3H), 2.43 (s, 3H),<br>2.58 (s, 3H), 3.81 (s, 3H), 4.42 (s, 2H),<br>6.92 (s, 1H), 7.29 (s, 1H), 8.36 (s, 1H)                                |
| 36                                   | 1.25 (t, 3H), 2.25 (s, 3H), 2.30 (s, 3H),<br>2.72 (k, 2H), 3.76 (s, 3H), 4.38 (s, 2H),<br>7.02 (k, 1H), 7.35 (d, 1H), 7.45 (d, 1H),<br>8.26 (s, 1H)               |
| 38                                   | 1.25 (s, 3H), 1.33 (s, 3H), 2.27 (s, 3H),<br>2.33 (s, 3H), 3.03 (m, 1H), 3.80 (s, 3H),<br>4.51 (s, 2H), 7.17 (k, 1H), 7.53 (d, 1H),<br>7.58 (d, 1H), 8.36 (s, 1H) |
| 39                                   | 2.22 (s, 3H), 2.31 (s, 3H), 3.81 (s, 3H),<br>4.72 (s, 2H), 7.76 (s, 2H), 8.23 (s, 1H)   |
| 40                                   | 1.41 (t, 3H), 2.30 (s, 3H), 2.35 (s, 3H),<br>3.82 (s, 3H), 4.10 (k, 2H), 4.39 (s, 2H),<br>6.92 (k, 1H), 7.14 (d, 1H), 7.52 (d, 1H),<br>8.40 (s, 1H)               |
| 41                                   | 2.16 (s, 3H), 2.26 (s, 3H), 3.71 (s, 3H),<br>4.68 (s, 2H), 7.23 (k, 1H), 7.43 (d, 1H),<br>7.65 (d, 1H), 8.18 (s, 1H)  |
| 42                                   | 3.80 (s, 3H), 3.83 (s, 3H), 4.50 (s, 2H),<br>6.90 (k, 1H), 7.15 (d, 1H), 7.24 (m, 2H),<br>7.53 (d, 1H), 8.23 (k, 1H)  |
| 43                                   | 2.33 (s, 3H), 2.35 (s, 3H), 4.80 (s, 2H),<br>7.19 (m, 2H), 7.52 (d, 1H), 7.58 (d, 1H),<br>8.34 (d, 1H)  |
| 44                                   | 2.34 (s, 6H), 3.85 (s, 3H), 4.51 (s, 2H),<br>6.89 (k, 1H), 7.15 (d, 1H), 7.15 (d, 1H),<br>7.53 (d, 1H), 8.41 (d, 1H)  |
| 45                                   | 2.16 (s, 6H), 2.38 (s, 3H), 2.53 (s, 3H),<br>4.46 (s, 2H), 6.86 (s, 1H), 6.99 (d, 1H),<br>7.25 (s, 1H), 8.20 (d, 1H)  |
| 46                                   | 2.26 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H),<br>4.70 (s, 2H), 6.87 (m, 2H), 7.10 (d, 1H),<br>7.48 (d, 1H), 8.42 (d, 1H)  |

TABLE 5 (cont.)

|    | Compound according<br>to example no. | NMR data<br>$\delta$  |
|----|--------------------------------------|---|
| 5  |                                      |   |
|    | 47                                   | 2.36 (s, 6H), 2.65 (s, 3H), 3.97 (s, 3H),<br>4.50 (s, 2H), 7.17 (d, 1H), 7.84 (s, 1H),<br>8.24 (s, 1H), 8.41 (d, 1H)                                |
| 10 |                                      |   |
|    | 48                                   | 2.31 (s, 3H), 2.34 (s, 3H), 2.64 (s, 3H),<br>4.71 (s, 2H), 7.12 (d, 1H), 7.59 (d, 1H),<br>7.91 (k, 1H), 8.22 (d, 1H), 8.36 (d, 1H)                  |
| 15 |                                      |   |
|    | 49                                   | 1.41 (t, 3H), 2.27 (s, 3H), 2.31 (s, 3H),<br>3.87 (s, 3H), 3.94 (k, 2H), 4.41 (s, 2H),<br>6.89 (k, 1H), 7.12 (d, 1H), 7.50 (d, 1H),<br>8.35 (s, 1H) |
| 20 |                                      |   |
|    | 50                                   | 1.17 (t, 3H), 2.61 (k, 2H), 2.69 (s, 3H),<br>3.93 (s, 6H), 4.43 (s, 2H), 7.00 (s, 1H),<br>7.45 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H)                  |

25 The starting materials in the examples 1—50 were prepared in accordance with the following:

1) a substituted o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Syn. Vol. 30, p. 56) to form a corresponding substituted 2-mercaptobenzimidazole;

2) a substituted 2-chloromethylpyridine was prepared by reacting the corresponding 2-hydroxymethylpyridine with thionylchloride;

30 3) a substituted 2-chloromethylbenzimidazole was prepared by condensing the o-phenylenediamine with chloroacetic acid.

The following examples illustrate how the compounds of the formula I can be incorporated in pharmaceutical compositions:

#### 35 Example 51 Syrup

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

|    |  |         |
|----|--|---------|
| 40 | 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-5-(5-acetyl-6-methyl)benzimidazole · HCl | 2.0 g   |
|    | Saccharin  | 0.6 g   |
| 45 | Sugar  | 30.0 g  |
|    | Glycerin   | 5.0 g   |
|    | Flavouring agent   | 0.1 g   |
| 50 | Ethanol 96%  | 10.0 ml |
|    | Distilled water (sufficient to obtain a final volume of 100 ml)                          |         |

55 Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerine and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

60 The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

#### Example 52 Tablets

65 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthiol]-5-(5-methoxy)benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened

with 10% solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10,000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

5

#### Example 53

##### Tablets

Granules were prepared from 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-(5-carbomethoxy-6-methyl)benzimidazole base (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10,000 tablets. These tablets are first coated with a 10% alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatin (4%), and dyestuff (0.2%). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66% sugar syrup and polished with a solution of 10% carnauba wax in carbon tetrachloride.

15

#### Example 54

##### Solution for injection

2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole hydrochloride (1 g), sodium chloride (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

20

#### Biological tests

##### Gastric acid secretion inhibiting effect on conscious dogs

25

##### Test Method

Chronic gastric fistula dogs (Heidenhain pouch dogs) were used. These dogs have been surgically provided with a gastric cannula in the pouch. Following a 4 weeks' recovery period after surgery, tests were performed once a week on each dog. Food and water were withdrawn 18 hours before each test.

30

Gastric acid secretion was induced by continuous infusion of histamine at individual doses (100—300  $\mu\text{mol/kg, h}$ ), resulting in submaximal secretion of gastric acid. At least 2 hours after onset of stimulation, when the gastric acid secretion had reached a steady level, the test compounds in the form of free base suspended in 0.5% Methocel® (90 HG, 15,000, Dow Chem. corp.), were given orally by stomach tube. The gastric juice was collected by free flow from the gastric cannula in consecutive 30 minutes samples for 3 hours. The samples were titrated to pH 7.0 with 0.1 M NaOH using a Radio-meter automatic titrator and the acid output was calculated.

35

The per cent inhibition of acid secretion was calculated by comparing in each dog the acid output in the tests to the acid output in control tests when only the vehicle was given.

The test results are given in Table 6 below.

40

45

50

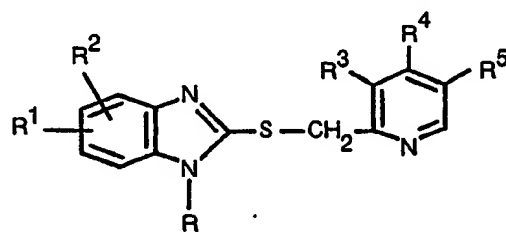
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60

65

TABLE 6

Gastric acid secretion inhibiting effect on conscious dogs

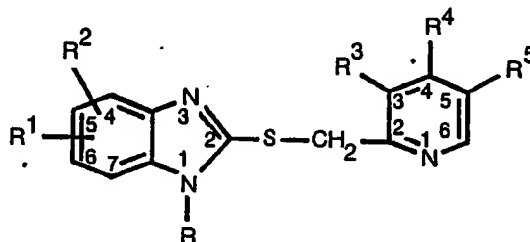
|  |                   |   |                 |                  |                 |  | Dose<br>( $\mu\text{mol/kg}$ ) | Effect<br>(% inhibition) |
|---|-------------------|---|-----------------|------------------|-----------------|--|--------------------------------|--------------------------|
| R <sup>1</sup>  | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |  |                                |                          |
| 5-OCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 2                              | 75                       |
| 5-COOCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 8                              | 50                       |
| 5-COOCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 2                              | 80                       |
| 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 2                              | 35                       |
| 5-COCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 8                              | 90                       |
| 5-CH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |  | 2                              | 60                       |
| 5-COCH <sub>3</sub>   | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> |  | 8                              | 80                       |
| 5-OCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |  | 2                              | 75                       |

## Comment to the test results

It is seen in Table 6 that the tested compounds after oral administration exhibited a high inhibiting effect on the gastric secretion.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A pharmaceutical preparation containing as active ingredient a compound of the formula



or a therapeutically acceptable salt thereof, in which formula

R<sup>1</sup> and R<sup>2</sup> are the same or different and each selected from the group consisting of H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, alkyl containing 1—7 carbon atoms, halogen, alkoxy containing 1—5 carbon atoms, and alkanoyl containing 1—4 carbon atoms;

R is selected from the group consisting of H, alkanoyl containing 1—4 carbon atoms, and carboalkoxy containing 2—6 carbon atoms; and

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, which are the same or different, are each selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; provided that

a) at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is selected from the group consisting of CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and

b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

c) when R is H,  $R^1$  or  $R^2$  is  $CF_3$  and  $R^3$  and  $R^5$  are  $CH_3$  and/or H,  $R^4$  is not  $OCH_3$ ; optionally in association with a pharmaceutically acceptable carrier.

5 2. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, halogen, alkoxy having 1—3 carbon atoms, and alkanoyl having 1—4 carbon atoms; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ .

10 3. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $CH_3$ , Cl, Br,  $OCH_3$  and  $CH_3CO$ ; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of H,  $CH_3$ ,  $OCH_3$ , and  $OCH_2CH_2OCH_3$ .

15 4. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $CH_3$ ,  $OCH_3$ , and  $CH_3CO$ ; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of  $CH_3$  and  $OCH_3$ .

5. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 1—4 carbon atoms; R is H; and wherein  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and selected from the group consisting of H,  $CH_3$ ,  $OCH_3$ , and  $OC_2H_5$ .

25 6. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, halogen, alkoxy having 1—3 carbon atoms, and alkanoyl having 1—4 carbon atoms; R is H; and wherein  $R^3$  is  $CH_3$ ;  $R^4$  is  $OCH_3$  and  $R^5$  is  $CH_3$ .

7. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 30 1—4 carbon atoms; R is H; and wherein  $R^3$  is H,  $R^4$  is  $OCH_3$  and  $R^5$  is  $CH_3$ .

8. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 1—4 carbon atoms; R is H; and wherein  $R^3$  is  $CH_3$ ,  $R^4$  is  $OCH_3$  and  $R^5$  is H.

35 9. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 1—4 carbon atoms; R is H; and wherein  $R^3$  is H,  $R^4$  is  $OCH_3$  and  $R^5$  is H.

10. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 40 1—4 carbon atoms; R is H; and wherein  $R^3$  is  $CH_3$ ,  $R^4$  is H and  $R^5$  is  $CH_3$ .

11. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 45 1—4 carbon atoms; R is H; and wherein  $R^3$  is H,  $R^4$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ , and  $R^5$  is H.

12. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein  $R^1$  and  $R^2$  are the same or different and each selected from the group consisting of H,  $COOCH_3$ ,  $COOC_2H_5$ , alkyl having 1—4 carbon atoms, alkoxy having 1—3 carbon atoms, and alkanoyl having 50 1—4 carbon atoms; R is H; and wherein  $R^3$  is  $CH_3$ ,  $R^4$  is  $CH_3$  and  $R^5$  is  $CH_3$ .

13. A pharmaceutical preparation according to claim 1, containing as active ingredient a compound of the formula I wherein R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are combined as follows:

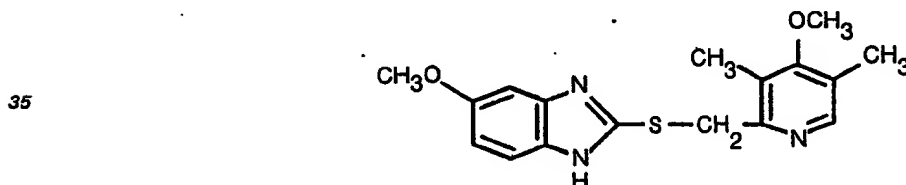
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65

|    | R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |
|----|----------------------|-------------------|---|-----------------|------------------|-----------------|
| 5  | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 10 | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 15 | 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
|    | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 20 | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
| 25 | 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
|    | 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

14. A pharmaceutical composition according to claim 1, containing as active ingredient a compound of the formula

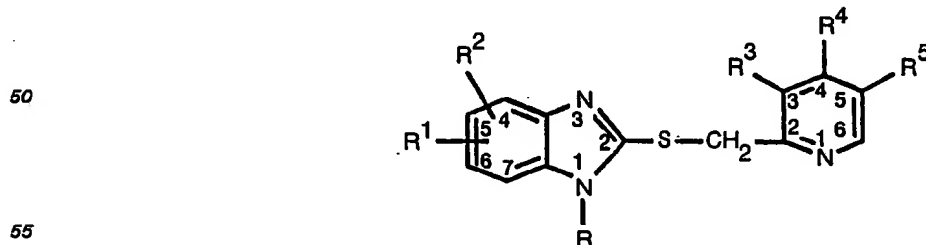


40 or a therapeutically acceptable salt thereof.

15. A compound as defined in any of claims 1—14, or a therapeutically acceptable salt thereof, for use in inhibiting gastric acid secretion in mammals and man.

16. A compound as defined in any of claims 1—14, or a therapeutically acceptable salt thereof, for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

45 17. A compound of the formula



and therapeutically acceptable salts thereof, in which formula

60 R<sup>1</sup> and R<sup>2</sup> are the same or different and each selected from the group consisting of H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, alkyl containing 1—7 carbon atoms, halogen, alkoxy containing 1—5 carbon atoms, and alkanoyl containing 1—4 carbon atoms;

R is selected from the group consisting of H; alkanoyl containing 1—4 carbon atoms, and carboalkoxy containing 2—6 carbon atoms;

65 and R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, which are the same or different, are each selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; provided that

a) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is selected from the group consisting of  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ , and

b) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining radical  $R^3$ ,  $R^4$  or  $R^5$  is selected from the group consisting of  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , and  $OCH_2CH_2OCH_2CH_3$ ; and provided that

5 i) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$  when R is alkanoyl containing 1—4 carbon atoms or carboalkoxy containing 2—6 carbon atoms and  $R^1$  and  $R^2$  have the definition given above;

ii) at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $C_2H_5$  when R is hydrogen and  $R^1$  and  $R^2$  have the definition given above;

10 iii) when two of  $R^3$ ,  $R^4$  and  $R^5$  are H, then the remaining of  $R^3$ ,  $R^4$  and  $R^5$  is  $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$  and R is alkanoyl containing 1—4 carbon atoms or carboalkoxy containing 2—6 carbon atoms and  $R^1$  and  $R^2$  have the definition given above;

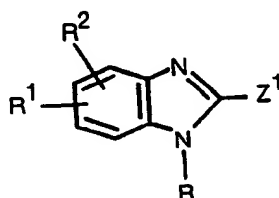
iv) when R is H, and  $R^1$  and  $R^2$  have the definition given above, then  $R^1$  and/or  $R^2$  is  $NO_2$ ; or

v) when R is H,  $R^1$  or  $R^2$  is  $CF_3$  and  $R^3$  and  $R^5$  are  $CH_3$  and/or H then  $R^4$  is not  $OCH_3$ .

15 18. A compound according to claim 17 or a therapeutically acceptable salt thereof, wherein R is H,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are as defined in claim 17, and wherein  $R^4$  is  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  or  $OCH_2CH_2OCH_2CH_3$ .

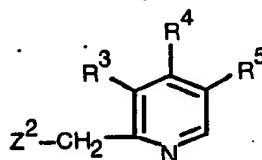
19. A process for the preparation of a compound according to any of claims 17—18, by

A. reacting a compound of the formula



II

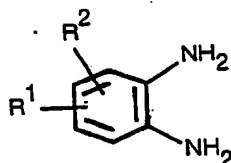
with a compound of the formula



III

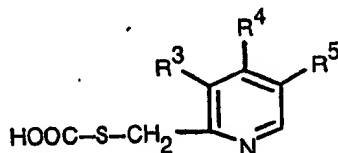
40 in which formula R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined previously and wherein one of  $Z^1$  and  $Z^2$  is SH and the other of  $Z^1$  and  $Z^2$  is a leaving group;

B. for the preparation of a compound of the formula I wherein R is H, reacting a compound of the formula



IV

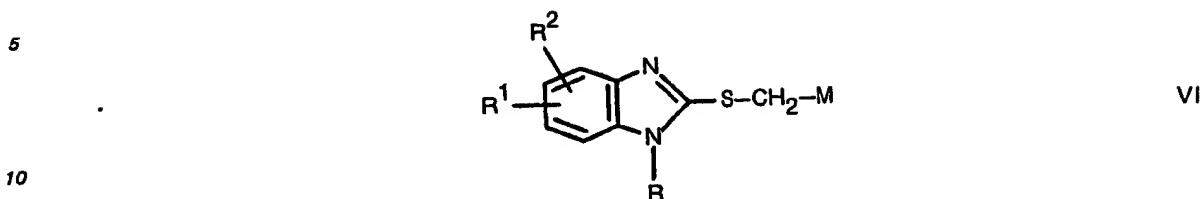
wherein  $R^1$  and  $R^2$  have the same meaning as given above, with a compound of the formula



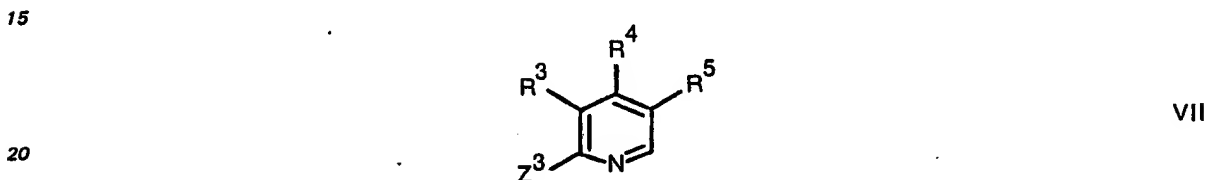
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65 wherein  $R^3$ ,  $R^4$  and  $R^5$  have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

C. reacting a compound of the formula

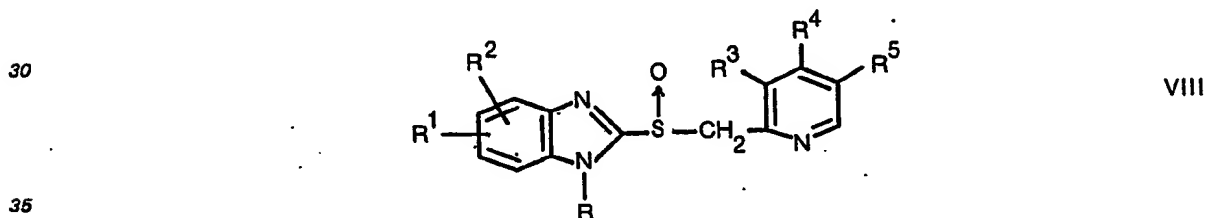


wherein R, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and M is K, Na or Li, with a compound of formula



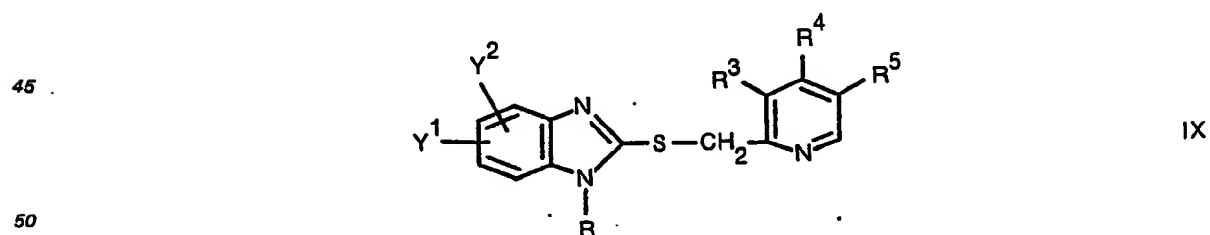
wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meaning given above and Z<sup>3</sup> is a reactive esterified hydroxy group, to the formation of a compound of the formula I;

D. reduction of a compound of the formula



to the formation of a compound of the formula I;

E. for the preparation of a compound of the formula I wherein the radicals R<sup>1</sup> and/or R<sup>2</sup> is COOCH<sub>3</sub> or COOC<sub>2</sub>H<sub>5</sub>, reacting a compound of the formula



wherein R, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> are as defined above and wherein Y<sup>1</sup> is —COOH, or a functionally equivalent derivative thereof, and Y<sup>2</sup> is —COOH, or a functionally equivalent derivative thereof, or R<sup>1</sup>, with



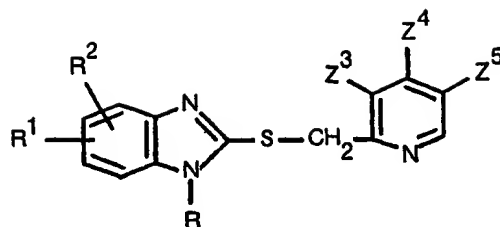
or



or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein R<sup>1</sup> and/or R<sup>2</sup> is CH<sub>3</sub>COO or CH<sub>3</sub>CH<sub>2</sub>COO;

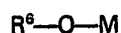
F. for the preparation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, reacting a compound of the formula





XII

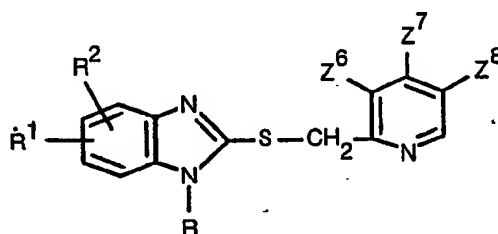
wherein R, R<sup>1</sup> and R<sup>2</sup> are as defined above and Z<sup>3</sup>, Z<sup>4</sup> and Z<sup>5</sup> represent either R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> respectively, or halogen such as Cl, Br, F or I, or NO<sub>2</sub>, whereby at least one of Z<sup>3</sup>, Z<sup>4</sup> and Z<sup>5</sup> represents halogen or NO<sub>2</sub>, with a compound of the formula



XIII

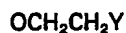
wherein R<sup>6</sup> is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

G. for the preparation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> reacting a compound of the formula



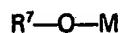
XIV

wherein R, R<sup>1</sup> and R<sup>2</sup> are as defined above and Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represent either R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, respectively, or a radical



XV

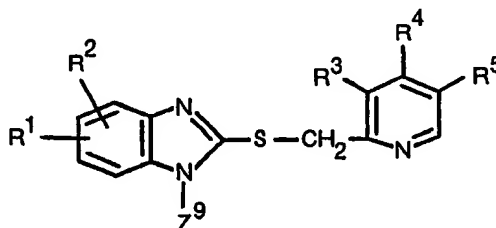
where Y is halogen, whereby at least one of Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represents OCH<sub>2</sub>CH<sub>2</sub>Y, with a compound of the formula



XVI

wherein R<sup>7</sup> is CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub> and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

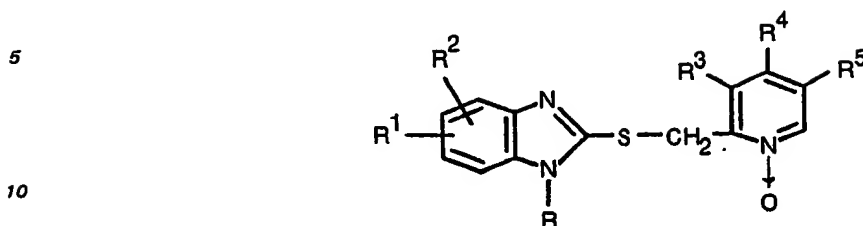
H. for the preparation of a compound of the formula I wherein R is H, hydrolyzing a compound of the formula



XVII

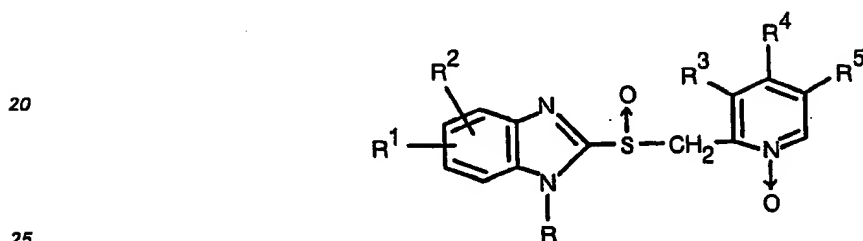
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above and Z<sup>9</sup> is an alkyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein R is H;

I. reduction of a compound of the formula



to the formation of a compound of the formula I;

15 J. reduction of a compound of the formula

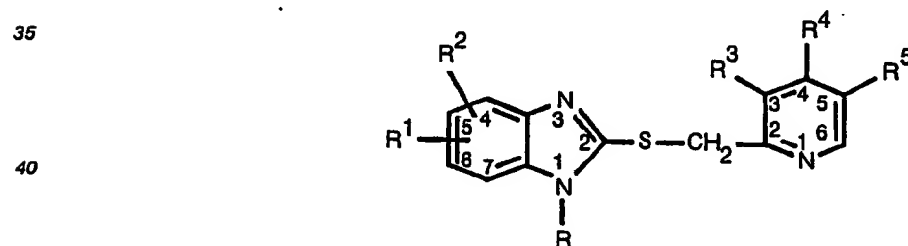


to the formation of a compound of the formula I;

whereafter, if desired, the compound thus obtained is converted to a therapeutically acceptable salt.

30 **Claims for the Contracting State: AT**

1. A process for the preparation of a compound of the formula



45 and therapeutically acceptable salts thereof, in which formula

R<sup>1</sup> and R<sup>2</sup> are the same or different and each selected from the group consisting of H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, alkyl containing 1—7 carbon atoms, halogen, alkoxy containing 1—5 carbon atoms, and alkanoyl containing 1—4 carbon atoms;

R is selected from the group consisting of H, alkanoyl containing 1—4 carbon atoms, and carboalkoxy containing 2—6 carbon atoms; and

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup>, which are the same or different, are each selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; provided that

a) at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is selected from the group consisting of CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and

55 b) when two of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are H, then the remaining radical R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is selected from the group consisting of OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; and provided that

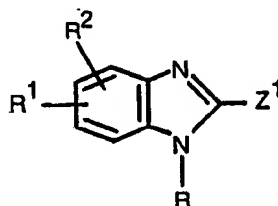
i) at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> when R is alkanoyl containing 1—4 carbon atoms or carboalkoxy containing 2—6 carbon atoms and R<sup>1</sup> and R<sup>2</sup> have the definition given above;

60 ii) at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is C<sub>2</sub>H<sub>5</sub> when R is hydrogen and R<sup>1</sup> and R<sup>2</sup> have the definition given above;

iii) when two of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are H, then the remaining of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> and R is alkanoyl containing 1—4 carbon atoms or carboalkoxy containing 2—6 carbon atoms and R<sup>1</sup> and R<sup>2</sup> have the definition given above;

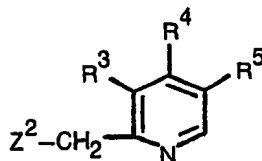
65 iv) when R is H, and R<sup>1</sup> and R<sup>2</sup> have the definition given above, then R<sup>1</sup> and/or R<sup>2</sup> is NO<sub>2</sub>; or

v) when R is H, R<sup>1</sup> or R<sup>2</sup> is CF<sub>3</sub> and R<sup>3</sup> and R<sup>5</sup> are CH<sub>3</sub> and/or H then R<sup>4</sup> is not OCH<sub>3</sub>, by  
A. reacting a compound of the formula



II

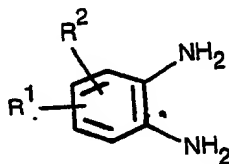
with a compound of the formula



III

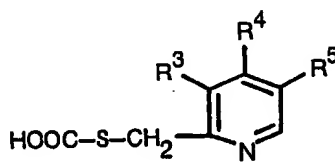
in which formula R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined previously and wherein one of Z<sup>1</sup> and Z<sup>2</sup> is SH and the other of Z<sup>1</sup> and Z<sup>2</sup> is a leaving group;

B. for the preparation of a compound of the formula I wherein R is H, reacting a compound of the formula



IV

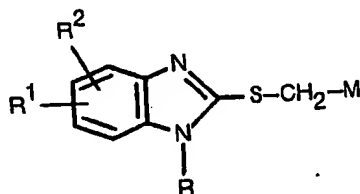
wherein R<sup>1</sup> and R<sup>2</sup> have the same meaning as given above, with a compound of the formula



V

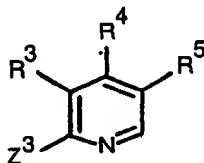
wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the same meaning as given above, to the formation of a compound of the formula I wherein R is H;

C. reacting a compound of the formula



VI

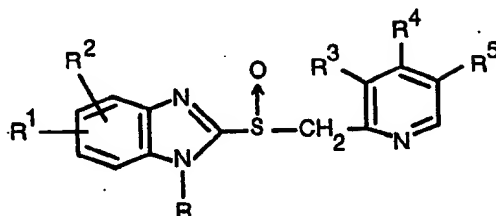
wherein R, R<sup>1</sup> and R<sup>2</sup> have the meaning given above and M is K, Na or Li, with a compound of formula



VII

wherein  $R^3$ ,  $R^4$  and  $R^5$  have the meaning given above and  $Z^3$  is a reactive esterified hydroxy group, to the formation of a compound of the formula I;

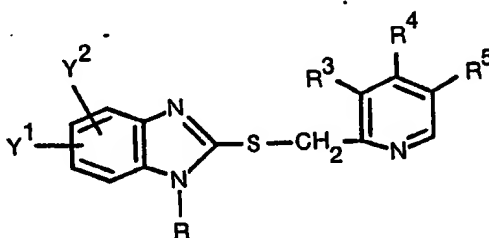
D. reduction of a compound of the formula



VIII

15 to the formation of a compound of the formula I.

E. for the preparation of a compound of the formula I wherein the radicals  $R^1$  and/or  $R^2$  is  $\text{COOCH}_3$  or  $\text{COOC}_2\text{H}_5$ , reacting a compound of the formula



IX

30 wherein  $R$ ,  $R^3$ ,  $R^4$  or  $R^5$  are as defined above and wherein  $Y^1$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, and  $Y^2$  is  $-\text{COOH}$ , or a functionally equivalent derivative thereof, or  $R^1$ , with



X

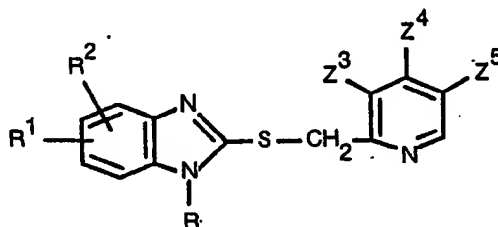
35 or



XI

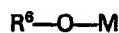
40 or a functionally equivalent derivative thereof, to the formation of a compound of the formula I wherein  $R^1$  and/or  $R^2$  is  $\text{CH}_3\text{COO}$  or  $\text{CH}_3\text{CH}_2\text{COO}$ ;

F. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , reacting a compound of the formula



XII

55 wherein  $R$ ,  $R^1$  and  $R^2$  are as defined above and  $Z^3$ ,  $Z^4$  and  $Z^5$  represent either  $R^3$ ,  $R^4$  and  $R^5$  respectively, or halogen such as  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{F}$  or  $\text{I}$ , or  $\text{NO}_2$ , whereby at least one of  $Z^3$ ,  $Z^4$  and  $Z^5$  represents halogen or  $\text{NO}_2$ , with a compound of the formula

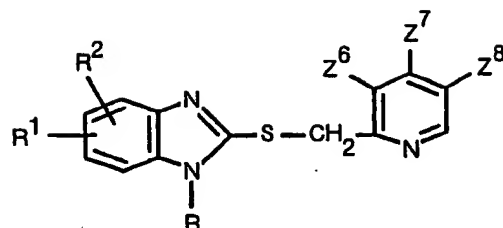


XIII

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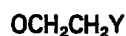
wherein  $R^6$  is  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_3$  or  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , and  $\text{M}$  is  $\text{Na}$ ,  $\text{K}$  or  $\text{Li}$ , to the formation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ;

65 G. for the preparation of a compound of the formula I wherein at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  reacting a compound of the formula



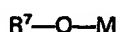
XIV

wherein R, R<sup>1</sup> and R<sup>2</sup> are as defined above and Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represent either R<sup>3</sup>, R<sup>4</sup> and R<sup>6</sup>, respectively, or a radical



XV

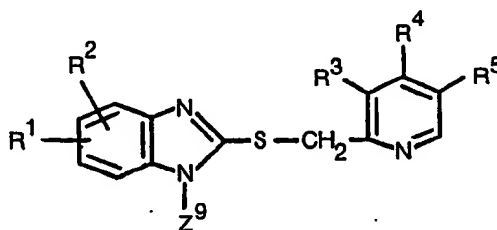
where Y is halogen, whereby at least one of Z<sup>6</sup>, Z<sup>7</sup> and Z<sup>8</sup> represents OCH<sub>2</sub>CH<sub>2</sub>Y, with a compound of the formula



XVI

wherein R<sup>7</sup> is CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub> and M is Na, K or Li, to the formation of a compound of the formula I wherein at least one of R<sup>3</sup>, R<sup>4</sup> and R<sup>6</sup> is OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

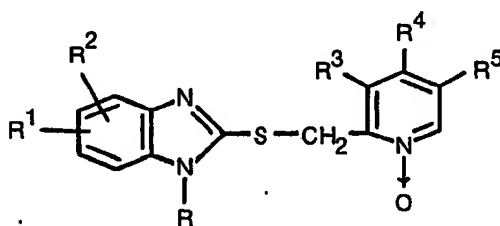
H. for the preparation of a compound of the formula I wherein R is H, hydrolyzing a compound of the formula



XVII

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above and Z<sup>9</sup> is an alkanoyl group or a carboalkoxy group, to the formation of a compound of the formula I wherein R is H;

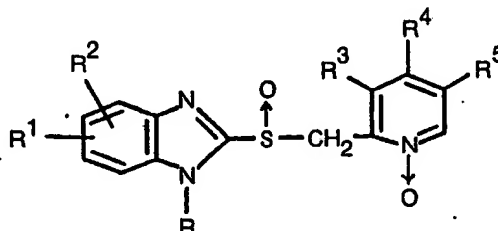
I. reduction of a compound of the formula



XVIII

to the formation of a compound of the formula I;

J. reduction of a compound of the formula



XIX

to the formation of a compound of the formula I;

whereafter, if desired, the compound of the formula I thus obtained is converted to a therapeutically acceptable salt.

2. A process according to claim 1 for the preparation of a compound as defined in claim 1, or a therapeutically acceptable salt thereof wherein R is H; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> are as defined in claim 1; and wherein R<sup>4</sup> is OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>.

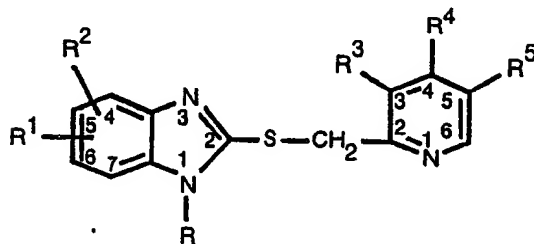
Pat ntanspruch für di V rtragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Pharmazeutische Präparation, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel

5

10

15



in welcher Formel

R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, Alkyl mit 1—7 Kohlenstoffatomen, Halogen, Alkoxy mit 1—5 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen;

20 R ausgewählt ist aus der Gruppe bestehend aus H, Alkanoyl mit 1—4 Kohlenstoffatomen und Carboalkoxy mit 2—6 Kohlenstoffatomen; und

R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup>, welche gleich oder verschieden sind, jeweils ausgewählt sind aus der Gruppe bestehend aus H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> und OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; mit der Maßgabe, daß

25 a) wenigstens eines von R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> ausgewählt ist aus der Gruppe bestehend aus CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> und OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> und

b) wenn zwei von R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> H sind, ist das verbleibende Radikal R<sup>3</sup>, R<sup>4</sup> oder R<sup>5</sup> ausgewählt aus der Gruppe bestehend aus OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> und OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; und

30 c) wenn R für H steht, R<sup>1</sup> oder R<sup>2</sup> CF<sub>3</sub> darstellt und R<sup>3</sup> und R<sup>5</sup> CH<sub>3</sub> und/oder H repräsentieren, ist R<sup>4</sup> nicht OCH<sub>3</sub>; oder ein therapeutisch akzeptables Salz davon, gewünschtenfalls zusammen mit einem pharmazeutisch akzeptablen Träger, umfaßt.

2. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, COOC<sub>2</sub>H<sub>5</sub>, Alkyl mit 1—4 Kohlenstoffatomen, Halogen, Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht; und worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> und OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, enthält.

3. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, CH<sub>3</sub>, Cl, Br, OCH<sub>3</sub> und CH<sub>3</sub>CO; R für H steht; und worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus H, CH<sub>3</sub>, OCH<sub>3</sub> und OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, enthält.

4. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, CH<sub>3</sub>, OCH<sub>3</sub> und CH<sub>3</sub>CO; R für H steht; und worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus CH<sub>3</sub> und OCH<sub>3</sub>, enthält.

5. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, Alkyl mit 1—4 Kohlenstoffatomen, Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht; und worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus H, CH<sub>3</sub>, OCH<sub>3</sub> und OC<sub>2</sub>H<sub>5</sub>, enthält.

6. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, COOC<sub>2</sub>H<sub>5</sub>, Alkyl mit 1—4 Kohlenstoffatomen, Halogen, Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht; und worin R<sup>3</sup> CH<sub>3</sub> darstellt; R<sup>4</sup> OCH<sub>3</sub> ist und R<sup>5</sup> CH<sub>3</sub> repräsentiert, enthält.

7. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, COOC<sub>2</sub>H<sub>5</sub>, Alkyl mit 1—4 Kohlenstoffatomen, Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht und worin R<sup>3</sup> H ist, R<sup>4</sup> OCH<sub>3</sub> repräsentiert und R<sup>5</sup> CH<sub>3</sub> darstellt, enthält.

8. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung der Formel I, worin R<sup>1</sup> und R<sup>2</sup> gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H, COOCH<sub>3</sub>, COOC<sub>2</sub>H<sub>5</sub>, Alkyl mit 1—4 Kohlenstoffatomen, Alkoxy

mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht; und worin  $R^3$   $\text{CH}_3$  ist,  $R^4$   $\text{OCH}_3$  darstellt und  $R^5$  H ist, enthält.

9. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives  
 5 Ingrediens eine Verbindung der Formel I, worin  $R^1$  und  $R^2$  gleich oder verschieden sind und jed s aus-  
 gewählt ist aus der Gruppe bestehend aus H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , Alkyl mit 1—4 Kohlenstoffatom n, Alkoxy  
 mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatom n; R H ist; und worin  $R^3$  für H steht,  $R^4$   
 $\text{OCH}_3$  darstellt und  $R^5$  H ist, enthält.

10. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives  
 10 Ingrediens eine Verbindung der Formel I, worin  $R^1$  und  $R^2$  gleich oder verschieden sind und jedes  
 ausgewählt ist aus der Gruppe bestehend aus H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , Alkyl mit 1—4 Kohlenstoffatomen,  
 Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen, R für H steht; und worin  $R^3$   
 $\text{CH}_3$  darstellt,  $R^4$  H ist und  $R^5$   $\text{CH}_3$  repräsentiert, enthält.

11. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives  
 15 Ingrediens eine Verbindung der Formel I, worin  $R^1$  und  $R^2$  gleich oder verschieden sind und jedes  
 ausgewählt ist aus der Gruppe bestehend aus H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , Alkyl mit 1—4 Kohlenstoffatomen,  
 Alkoxy mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht, und worin  $R^3$   
 H ist,  $R^4$   $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  repräsentiert und  $R^5$  H darstellt, enthält.

12. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives  
 20 Ingrediens eine Verbindung der Formel I, worin  $R^1$  und  $R^2$  gleich oder verschieden sind und jedes aus-  
 gewählt ist aus der Gruppe bestehend aus H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , Alkyl mit 1—4 Kohlenstoffatomen, Alkoxy  
 mit 1—3 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R für H steht; und worin  $R^3$   $\text{CH}_3$  ist,  
 $R^4$   $\text{CH}_3$  darstellt und  $R^5$   $\text{CH}_3$  repräsentiert, enthält.

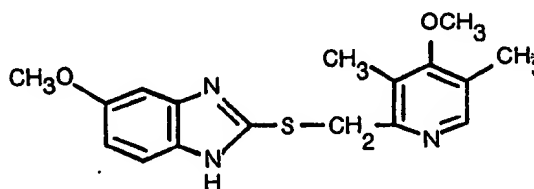
13. Pharmazeutische Präparation nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktiv s  
 25 Ingrediens eine Verbindung der Formel I, worin  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie folgt kombiniert sind:

|    | $R^1$               | $R^2$            | R | $R^3$         | $R^4$          | $R^5$         |
|----|---------------------|------------------|---|---------------|----------------|---------------|
| 30 | 5- $\text{OCH}_3$   | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | 5- $\text{COOCH}_3$ | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | 5- $\text{COOCH}_3$ | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
| 35 | 5- $\text{COCH}_3$  | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | 5- $\text{COCH}_3$  | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
|    | 5- $\text{CH}_3$    | H                | H | $\text{CH}_3$ | $\text{OCH}_3$ | $\text{CH}_3$ |
| 40 | 5- $\text{COCH}_3$  | 6- $\text{CH}_3$ | H | H             | $\text{CH}_3$  | $\text{CH}_3$ |
|    | 5- $\text{OCH}_3$   | H                | H | $\text{CH}_3$ | $\text{CH}_3$  | $\text{CH}_3$ |
| 45 | 5- $\text{COCH}_3$  | 6- $\text{CH}_3$ | H | H             | $\text{OCH}_3$ | H             |
|    | 5- $\text{COOCH}_3$ | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{OCH}_3$ | H             |
|    | 5- $\text{COCH}_3$  | 6- $\text{CH}_3$ | H | $\text{CH}_3$ | $\text{CH}_3$  | $\text{CH}_3$ |
| 50 | 5- $\text{COOCH}_3$ | 6- $\text{CH}_3$ | H | H             | $\text{OCH}_3$ | H             |

55 enthält.

14. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß sie als aktives  
 Ingrediens eine Verbindung der Formel

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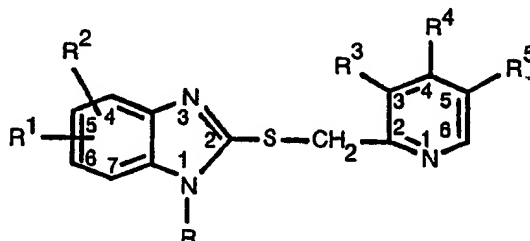
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oder ein therapeutisch akzeptables Salz davon enthält.

15. Verbindung nach irgendeinem der Ansprüche 1—14 oder ein therapeutisch akzeptables Salz davon, zur Verwendung bei der Hemmung der Magensäuresekretion bei Säugetieren und Menschen.

16. Verbindung nach irgendeinem der Ansprüche 1—14 oder ein therapeutisch akzeptables Salz davon, zur Verwendung bei der Behandlung von gastrointestinalen entzündlichen Erkrankungen bei Säugtieren und Menschen.

17. Verbindung der Formel, dadurch gekennzeichnet, daß



in dieser Formel  $R^1$  und  $R^2$  gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , Alkyl mit 1—7 Kohlenstoffatomen, Halogen, Alkoxy mit 1—5 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen; R ausgewählt ist aus der Gruppe bestehend aus H; Alkanoyl mit 1—4 Kohlenstoffatomen und Carboalkoxy mit 2—6 Kohlenstoffatomen; und  $R^3$ ,  $R^4$  und  $R^5$ , welche gleich oder verschieden sind, jeweils ausgewählt sind aus der Gruppe bestehend aus H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$ ; mit der Maßgabe, daß

a) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$  ausgewählt ist aus der Gruppe bestehend aus  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$  und

b) wenn zwei von  $R^3$ ,  $R^4$  und  $R^5$  H sind, ist das verbleibende Radikal  $R^3$ ,  $R^4$  oder  $R^5$  ausgewählt aus der Gruppe bestehend aus  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$ ; und mit der Maßgabe, daß

i) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$  darstellt, wenn R für Alkanoyl mit 1—4 Kohlenstoffatomen oder Carboalkoxy mit 2—6 Kohlenstoffatomen steht und  $R^1$  und  $R^2$  wie oben definiert sind;

ii) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $C_2H_5$  darstellt, wenn R für Wasserstoff steht und  $R^1$  und  $R^2$  wie oben definiert sind.

iii) wenn zwei von  $R^3$ ,  $R^4$  und  $R^5$  Wasserstoff sind, ist das Verbleibende von  $R^3$ ,  $R^4$  und  $R^5$   $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$ , und R repräsentiert Alkanoyl mit 1—4 Kohlenstoffatomen oder Carboalkoxy mit 2—6 Kohlenstoffatomen, und  $R^1$  und  $R^2$  haben die oben angegebene Bedeutung.

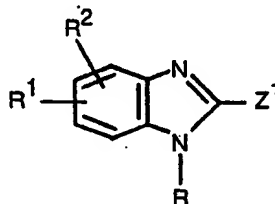
iv) wenn R H ist, und  $R^1$  und  $R^2$  die oben angegebene Bedeutung haben, stehen  $R^1$  und/oder  $R^2$  für  $NO_2$ , oder

v) wenn R H ist,  $R^1$  oder  $R^2$  für  $CF_3$  steht und  $R^3$  und  $R^5$   $CH_3$  und/oder H sind, stellt  $R^4$  noch  $OCH_3$  dar, und therapeutisch akzeptablen Salze davon.

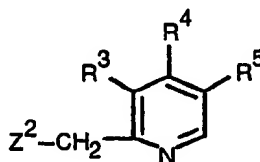
18. Verbindung nach Anspruch 17 oder ein therapeutisch akzeptables Salz davon, worin R H ist,  $R^1$ ,  $R^2$ ,  $R^3$  und  $R^5$  wie im Anspruch 17 definiert sind und worin  $R^4$   $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$  repräsentiert.

19. Verfahren zur Herstellung einer Verbindung nach irgendeinem der Ansprüche 17—18, dadurch gekennzeichnet, daß

A. eine Verbindung der Formel



mit einer Verbindung der Formel



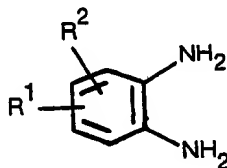


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in welcher Formel R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> die vorstehend Bedeutung haben, und worin eines von Z<sup>1</sup> und Z<sup>2</sup> für SH steht und das andere von Z<sup>1</sup> und Z<sup>2</sup> eine austretende Gruppe darstellt, umgesetzt wird;

B. zur Herstellung einer Verbindung der Formel I, worin R gleich H ist, eine Verbindung der Formel

5

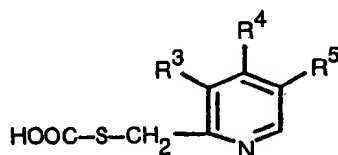


IV

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worin R<sup>1</sup> und R<sup>2</sup> die oben angegebene Bedeutung haben, mit einer Verbindung der Formel

15



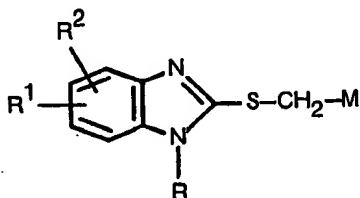
V

20

worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> die gleiche oben angegebene Bedeutung haben, zur Bildung einer Verbindung der Formel I, worin R für H steht, umgesetzt wird;

25 C. eine Verbindung der Formel

30

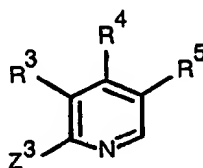


VI

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worin R, R<sup>1</sup> und R<sup>2</sup> wie oben definiert sind, und M für K, Na oder Li steht, mit einer Verbindung der Formel I

40



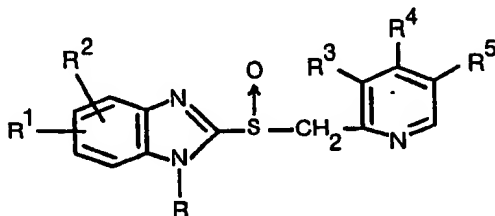
VII

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50 worin R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> die oben angegebene Bedeutung haben und Z<sup>3</sup> eine reaktive veresterte Hydroxygruppe ist, zur Bildung einer Verbindung der Formel I umgesetzt wird;

D. eine Verbindung der Formel

55

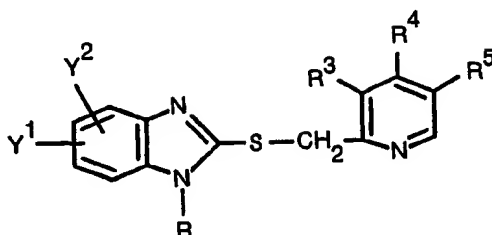


VIII

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65 zur Bildung einer Verbindung der Formel I reduziert wird.

E. zur Herstellung einer Verbindung der Formel I, worin die Radikale  $R^1$  und/oder  $R^2$   $\text{COOCH}_3$  oder  $\text{COOC}_2\text{H}_5$  sind, eine Verbindung der Formel



IX

15 worin  $R$ ,  $R^2$ ,  $R^4$  oder  $R^5$  wie oben definiert sind, und worin  $Y^1$  für  $-\text{COOH}$  oder ein funktionell äquivalentes Derivat davon steht, und  $Y^2$   $-\text{COOH}$  oder ein funktionell äquivalentes Derivat davon oder  $R^1$  repräsentiert, mit



X

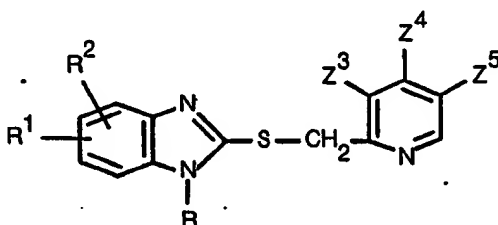
oder



XI

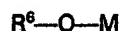
25 oder einem funktionell äquivalentem Derivat davon zur Bildung einer Verbindung der Formel I, worin  $R^1$  und/oder  $R^2$  für  $\text{CH}_3\text{COO}$  oder  $\text{CH}_3\text{CH}_2\text{COO}$  stehen, umgesetzt wird;

F. zur Herstellung einer Verbindung der Formel I, worin wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  darstellt, eine Verbindung der Formel



XII

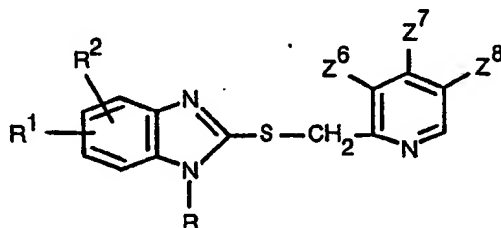
40 worin  $R$ ,  $R^1$  und  $R^2$  wie oben definiert sind und  $Z^3$ ,  $Z^4$  und  $Z^5$  jeweils entweder  $R^3$ ,  $R^4$  und  $R^5$  oder Halogen, wie Cl, Br, F oder J, oder  $\text{NO}_2$  repräsentiert, wobei wenigstens eines von  $Z^3$ ,  $Z^4$  und  $Z^5$  Halogen oder  $\text{NO}_2$  darstellt, mit einer Verbindung der Formel



XIII,

45 worin  $R^6$  für  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  steht, und  $\text{M}$  Na, K oder Li darstellt, zur Bildung einer Verbindung der Formel I, worin wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  repräsentiert, umgesetzt wird;

50 G. zur Herstellung einer Verbindung der Formel I, worin wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$  für  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  steht, eine Verbindung der Formel



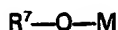
XIV

worin  $R$ ,  $R^1$  und  $R^2$  wie oben definiert sind, und  $Z^6$ ,  $Z^7$  und  $Z^8$  jeweils entweder  $R^3$ ,  $R^4$  und  $R^5$  oder ein Radikal



XV,

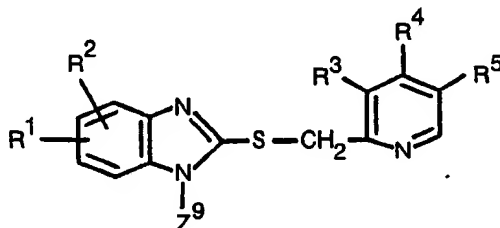
worin Y Halogen ist, wobei wenigstens eines von  $Z^6$ ,  $Z^7$  und  $Z^8$   $OCH_2CH_2Y$  repräsentiert, dargestellt, mit einer Verbindung der Formel



XVI,

worin  $R^7$  für  $CH_3$  oder  $CH_2CH_3$  steht, und M Na, K oder Li darstellt, zur Bildung einer Verbindung der Formel I, worin wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$  repräsentiert, umgesetzt wird;

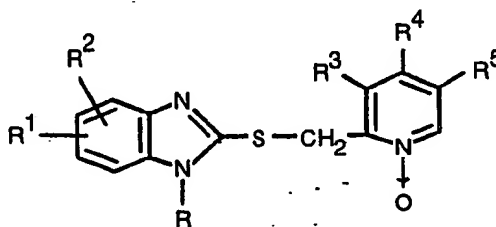
H. zur Herstellung einer Verbindung der Formel I, worin R für H steht, eine Verbindung der Formel



XVII

worin  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind und  $Z^9$  eine Alkanoylgruppe oder eine Carboalkoxygruppe darstellt, zur Bildung einer Verbindung der Formel I, worin R für H steht, hydrolysiert wird;

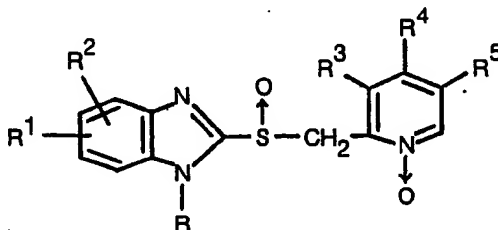
I. eine Verbindung der Formel



XVIII

zur Bildung einer Verbindung der Formel I reduziert wird;

J. eine Verbindung der Formel

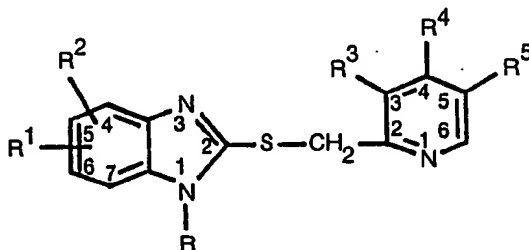


XIX

zur Bildung einer Verbindung der Formel I reduziert wird; wonach gewünschtenfalls die so erhaltene Verbindung in ein therapeutisch akzeptables Salz übergeführt wird.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel



und therapeutisch akzeptable Salze davon, in welcher Formel

$R^1$  und  $R^2$  gleich oder verschieden sind und jedes ausgewählt ist aus der Gruppe bestehend aus H,  $CF_3$ ,  $NO_2$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ , Alkyl mit 1—7 Kohlenstoffatomen, Halogen, Alkoxy mit 1—5 Kohlenstoffatomen und Alkanoyl mit 1—4 Kohlenstoffatomen;

$R$  ausgewählt ist aus der Gruppe bestehend aus H, Alkanoyl mit 1—4 Kohlenstoffatomen und Carboalkoxy mit 2—6 Kohlenstoffatomen; und

$R^3$ ,  $R^4$  und  $R^5$ , welche gleich oder verschieden sind, jeweils ausgewählt sind aus der Gruppe bestehend aus H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$ ; mit der Maßgabe, daß

a) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$  ausgewählt ist aus der Gruppe bestehend aus  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$  und

b) wenn zwei von  $R^3$ ,  $R^4$  und  $R^5$  H sind, ist das verbleibende Radikal  $R^3$ ,  $R^4$  oder  $R^5$  ausgewählt aus der Gruppe bestehend aus  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  und  $OCH_2CH_2OCH_2CH_3$ ; und mit der Maßgabe, daß

i) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$  steht, wenn  $R$  Alkanoyl mit 1—4 Kohlenstoffatomen oder Carboalkoxy mit 2—6 Kohlenstoffatomen darstellt und  $R^1$  und  $R^2$  die obige Bedeutung haben;

ii) wenigstens eines von  $R^3$ ,  $R^4$  und  $R^5$   $C_2H_5$  repräsentiert, wenn  $R$  Wasserstoff ist und  $R^1$  und  $R^2$  die oben angegebene Bedeutung haben;

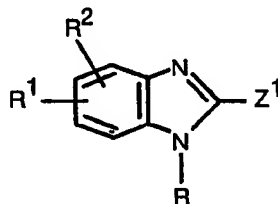
iii) wenn zwei von  $R^3$ ,  $R^4$  und  $R^5$  H darstellen, ist das Verbleibende von  $R^3$ ,  $R^4$  und  $R^5$   $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  oder  $OCH_2CH_2OCH_2CH_3$  und  $R$  ist Alkanoyl mit 1—4 Kohlenstoffatomen oder Carboalkoxy mit 2—6 Kohlenstoffatomen und  $R^1$  und  $R^2$  haben die obige Bedeutung;

iv) wenn  $R$  für H steht und  $R^1$  und  $R^2$  die oben angegebene Bedeutung haben, ist  $R^1$  und/oder  $R^2$   $NO_2$ ; oder

v) wenn  $R$  für H steht,  $R^1$  oder  $R^2$   $CF_3$  repräsentiert und  $R^3$  und  $R^5$   $CH_3$  und/oder H darstellen, steht  $R^4$  nicht für  $OCH_3$ ,

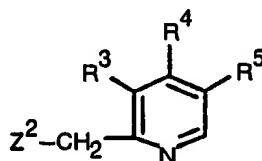
welches Verfahren dadurch gekennzeichnet ist, daß

A. eine Verbindung der Formel



II

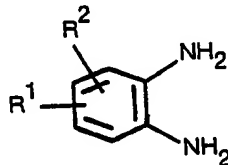
mit einer Verbindung der Formel



III

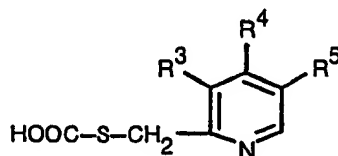
in welcher Formel  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie vorstehend definiert sind, und worin eines von  $Z^1$  und  $Z^2$  für SH steht und das andere von  $Z^1$  und  $Z^2$  eine austretende Gruppe ist, umgesetzt wird;

B. zur Herstellung einer Verbindung der Formel I, worin  $R$  für H steht, eine Verbindung der Formel



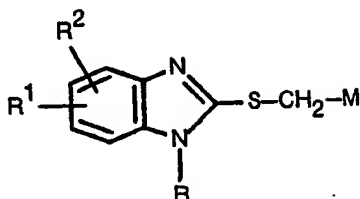
IV

worin  $R^1$  und  $R^2$  die gleiche Bedeutung wie oben haben, mit einer Verbindung der Formel



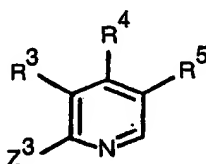
V

worin  $R^3$ ,  $R^4$  und  $R^5$  die gleiche Bedeutung wie oben haben, zur Bildung einer Verbindung der Formel I, worin R für H steht, umgesetzt wird;  
C. eine Verbindung der Formel



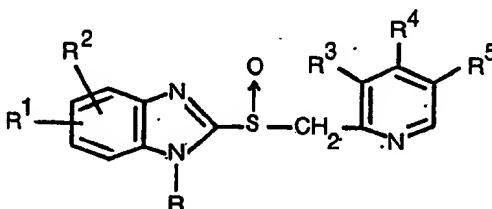
VI

worin R,  $R^1$  und  $R^2$  wie oben definiert sind und M für K, Na oder Li steht, mit einer Verbindung der Formel



VII

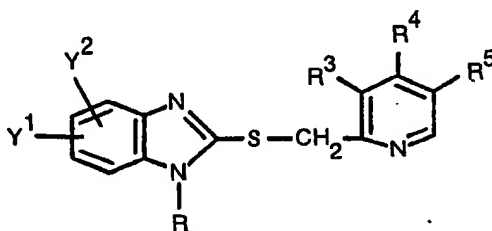
worin  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind und  $Z^3$  eine reaktive veresterte Hydroxygruppe ist, zur Bildung einer Verbindung der Formel I umgesetzt wird;  
D. eine Verbindung der Formel



VIII

zur Bildung einer Verbindung der Formel I reduziert wird;

E. zur Herstellung einer Verbindung der Formel I, worin die Radikale  $R^1$  und/oder  $R^2$   $\text{COOCH}_3$  oder  $\text{COOC}_2\text{H}_5$  stehen, eine Verbindung der Formel



IX

worin R,  $R^2$ ,  $R^4$  oder  $R^5$  wie oben definiert sind, und worin  $Y^1$  für  $-\text{COOH}$  oder ein funktionell äquivalentes Derivat davon steht und  $Y^2$   $-\text{COOH}$  oder ein funktionell äquivalentes Derivat davon oder  $R^1$  darstellt, mit



X

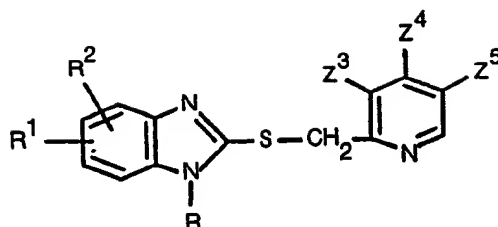
oder



XI

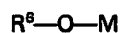
oder einem funktionell äquivalenten Derivat davon, zur Bildung einer Verbindung der Formel I, worin  $R^1$  und/oder  $R^2$  für  $\text{CH}_3\text{COO}$  oder  $\text{CH}_3\text{CH}_2\text{COO}$  darstellt, umgesetzt wird;

F. zur Herstellung einer Verbindung der Formel I, worin wenigstens eines von  $R^3$ ,  $R^4$  oder  $R^5$   $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  oder  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$  repräsentiert, eine Verbindung der Formel



XII

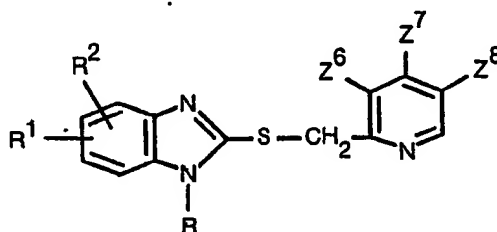
worin R, R<sup>1</sup> und R<sup>2</sup> wie oben definiert sind und Z<sup>3</sup>, Z<sup>4</sup> und Z<sup>5</sup> entweder jeweils R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> oder Halogen, wie Cl, Br, F oder J oder NO<sub>2</sub> repräsentieren, wobei wenigstens eines von Z<sup>3</sup>, Z<sup>4</sup> und Z<sup>5</sup> Halogen oder NO<sub>2</sub> repräsentiert, mit einer Verbindung der Formel



XIII,

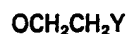
worin R<sup>6</sup> für CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> oder OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> steht und M Na, K oder Li darstellt, zur Bildung einer Verbindung der Formel I, worin wenigstens eines von R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> oder OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> darstellt, umgesetzt wird;

G. zur Herstellung einer Verbindung der Formel I, worin wenigstens eines von R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> für OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> oder OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> steht, eine Verbindung der Formel



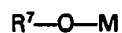
XIV

worin R, R<sup>1</sup> und R<sup>2</sup> wie oben definiert sind und Z<sup>6</sup>, Z<sup>7</sup> und Z<sup>8</sup> entweder jeweils R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> oder ein Radikal



XV,

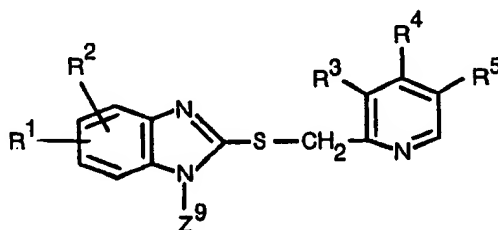
repräsentieren, worin Y Halogen ist, wobei wenigstens eines von Z<sup>6</sup>, Z<sup>7</sup> und Z<sup>8</sup> OCH<sub>2</sub>CH<sub>2</sub>Y repräsentiert, mit einer Verbindung der Formel



XVI,

worin R<sup>7</sup> für CH<sub>3</sub> oder CH<sub>2</sub>CH<sub>3</sub> steht und M Na, K oder Li ist, zur Bildung einer Verbindung der Formel I, worin wenigstens eines von R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> oder OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> darstellt, umgesetzt wird;

H. zur Herstellung einer Verbindung der Formel I, worin R für H steht, eine Verbindung der Formel



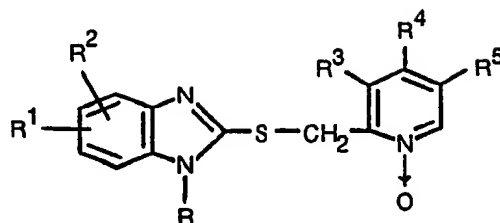
XVII

worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> wie oben definiert sind und Z<sup>9</sup> eine Alkanoylgruppe oder eine Carboalkoxygruppe darstellt, zur Bildung einer Verbindung der Formel I, worin R für H steht, hydrolysiert wird;

I. une Verbindung der Formel

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XVIII

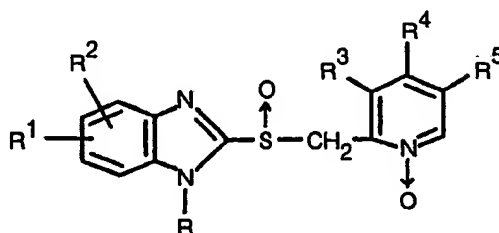
zur Bildung einer Verbindung der Formel I reduziert wird;

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J. eine Verbindung der Formel

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XIX

zur Bildung einer Verbindung der Formel I reduziert wird;

wonach, gewünschtenfalls, die so erhaltene Verbindung der Formel I in eine therapeutisch akzeptables Salz davon übergeführt wird.

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2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine in Anspruch 1 definierte Verbindung oder ein therapeutisch akzeptables Salz davon, worin R für H steht; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>5</sup> wie in Anspruch 1 definiert sind; und worin R<sup>4</sup> OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> oder OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> repräsentiert, hergestellt wird.

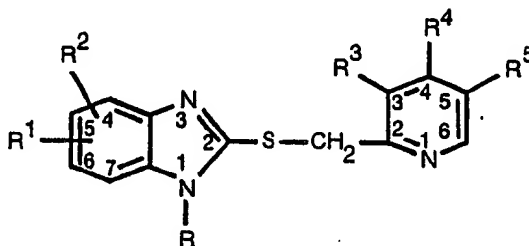
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Revendications pour les Etats Contractants: BE CH DE FR GB IT LI LU NL SE -

1. Composition pharmaceutique contenant, à titre de principe actif, un composé de formule:

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I

ou un sel thérapeutiquement acceptable de ce composé, formule dans laquelle:

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R<sup>1</sup> et R<sup>2</sup> sont identiques ou différents et choisis chacun dans l'ensemble constitué par H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, un groupe alkyle contenant 1 à 7 atomes de carbone, un atome d'halogène, un groupe alcoxy contenant 1 à 5 atomes de carbone, et un groupe alcanoyle contenant 1 à 4 atomes de carbone;

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R est choisi dans l'ensemble constitué par H, un groupe alcanoyle contenant 1 à 4 atomes de carbone et carboxalcoxy contenant 2 à 6 atomes de carbone; et

R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, identiques ou différents, sont choisis chacun dans l'ensemble constitué par H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, à la condition que:

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a) au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> soit choisi dans l'ensemble constitué par CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> et

b) quand deux des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représentent H, le radical restant R<sup>3</sup>, R<sup>4</sup> ou R<sup>5</sup> soit choisi dans l'ensemble constitué par OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; t

c) quand R représente H, R<sup>1</sup> ou R<sup>2</sup> représente CF<sub>3</sub> et R<sup>3</sup> et R<sup>5</sup> représentent CH<sub>3</sub> t/ou H, R<sup>4</sup> ne représente pas OCH<sub>3</sub>;

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éventuellement en association avec un excipient ou support pharmaceutiquement acceptable.

2. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques et différents et choisis chacun dans l'ensemble constitué par H,  $\text{COOCH}_3$ ,  $\text{COOC}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, un atome d'halogène, un groupe alcoxy ayant 1 à 3 atomes de carbone et un groupe alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H, et  $R^3$ ,  $R^4$  et  $R^5$  sont identiques ou différents et choisis dans l'ensemble constitué par H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  et  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ .
3. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOCH}_3$ ,  $\text{CH}_3$ , Cl, Br,  $\text{OCH}_3$  et  $\text{CH}_3\text{CO}$ ; R représente H; et  $R^3$ ,  $R^4$  et  $R^5$  sont identiques ou différents et choisis dans l'ensemble constitué par H,  $\text{CH}_3$ ,  $\text{OCH}_3$ , et  $\text{OCH}_2\text{CH}_2\text{OCH}_3$ .
4. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et choisis chacun dans l'ensemble constitué par H,  $\text{COOCH}_3$ ,  $\text{CH}_3$ ,  $\text{OCH}_3$  et  $\text{CH}_3\text{CO}$ ; R représente H; et  $R^3$ ,  $R^4$  et  $R^5$  sont identiques ou différents et choisis chacun parmi  $\text{CH}_3$  et  $\text{OCH}_3$ .
5. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOCH}_3$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$ ,  $R^4$  et  $R^5$  sont identiques ou différents et choisis dans l'ensemble constitué par H,  $\text{CH}_3$ ,  $\text{OCH}_3$  et  $\text{OC}_2\text{H}_5$ .
6. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, un atome d'halogène, un groupe alcoxy ayant 1 à 3 atomes de carbone et un groupe alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente  $\text{CH}_3$ ;  $R^4$  représente  $\text{OCH}_3$  et  $R^5$  représente  $\text{CH}_3$ .
7. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente H;  $R^4$  représente  $\text{OCH}_3$  et  $R^5$  représente  $\text{CH}_3$ .
8. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente  $\text{CH}_3$ ;  $R^4$  représente  $\text{OCH}_3$  et  $R^5$  représente H.
9. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente H,  $R^4$  représente  $\text{OCH}_3$  et  $R^5$  représente H.
10. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente  $\text{CH}_3$ ,  $R^4$  représente H et  $R^5$  représente  $\text{CH}_3$ .
11. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente H,  $R^4$  représente  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OCH}_2\text{CH}_2\text{OCH}_3$  ou  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ , et  $R^5$  représente H.
12. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I, dans laquelle  $R^1$  et  $R^2$  sont identiques ou différents et choisis chacun dans l'ensemble constitué par H,  $\text{COOC}_3$ ,  $\text{COOCH}_2\text{H}_5$ , un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 3 atomes de carbone et alcanoyloxy ayant 1 à 4 atomes de carbone; R représente H; et  $R^3$  représente  $\text{CH}_3$ ,  $R^4$  représente  $\text{CH}_3$  et  $R^5$  représente  $\text{CH}_3$ .
13. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule I dans laquelle R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont combinés comme suit:



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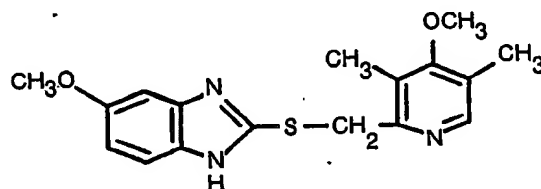
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| R <sup>1</sup>       | R <sup>2</sup>    | R | R <sup>3</sup>  | R <sup>4</sup>   | R <sup>5</sup>  |
|----------------------|-------------------|---|-----------------|------------------|-----------------|
| 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-COOCH <sub>3</sub> | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-COCH <sub>3</sub>  | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-CH <sub>3</sub>    | H                 | H | CH <sub>3</sub> | OCH <sub>3</sub> | CH <sub>3</sub> |
| 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | CH <sub>3</sub>  | CH <sub>3</sub> |
| 5-OCH <sub>3</sub>   | H                 | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |
| 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | OCH <sub>3</sub> | H               |
| 5-COCH <sub>3</sub>  | 6-CH <sub>3</sub> | H | CH <sub>3</sub> | CH <sub>3</sub>  | CH <sub>3</sub> |
| 5-COOCH <sub>3</sub> | 6-CH <sub>3</sub> | H | H               | OCH <sub>3</sub> | H               |

14. Composition pharmaceutique selon la revendication 1, contenant à titre de principe actif un composé de formule:

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ou un sel thérapeutiquement acceptable de ce composé.

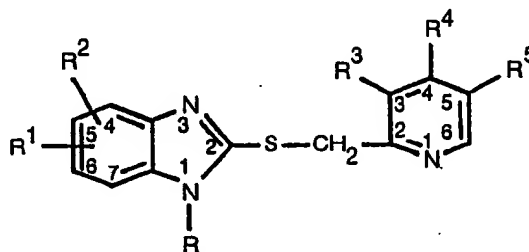
15. Composé selon la définition donnée dans l'une quelconque des revendications 1 à 14, ou un sel thérapeutiquement acceptable de ce composé, destiné à servir d'inhibiteur de la sécrétion des acides gastriques chez les mammifères et l'être humain.

16. Composé selon la définition donnée dans l'une quelconque des revendications 1 à 14, ou un sel thérapeutiquement acceptable de ce composé, destiné à servir au traitement des maladies inflammatoires gastro-intestinales des mammifères et êtres humains.

17. Composé de formule:

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et ses sels thérapeutiquement acceptables, formule dans laquelle:

R<sup>1</sup> et R<sup>2</sup> sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOCH<sub>2</sub>H<sub>5</sub>, un groupe alkyle contenant 1 à 7 atomes de carbone, un atome d'halogène, un groupe alcylique contenant 1 à 5 atomes de carbone, et un groupe alcanoyle contenant 1 à 4 atomes de carbone;

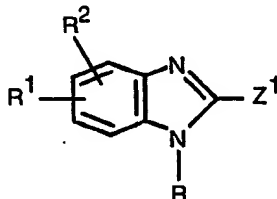
R est choisi dans l'ensemble constitué par H, un groupe alcanoyle contenant 1 à 4 atomes de carbone et carbalcoxy contenant 2 à 6 atomes de carbone; t

$R^3$ ,  $R^4$  et  $R^5$ , identiques ou différents, sont choisis chacun dans l'ensemble constitué par H,  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$ , et  $OCH_2CH_2OCH_2CH_3$ , à la condition que:

- a) au moins l'un des symboles  $R^3$ ,  $R^4$  et  $R^5$  soit choisi dans l'ensemble constitué par  $CH_3$ ,  $C_2H_5$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  et  $OCH_2CH_2OCH_2CH_3$  et
- b) quand deux des symboles  $R^3$ ,  $R^4$  et  $R^5$  représentent H, le radical  $R^3$ ,  $R^4$  ou  $R^5$  restant soit choisi dans l'ensemble constitué par  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  et  $OCH_2CH_2OCH_2CH_3$ ; et à la condition que:
  - i) au moins l'un des symboles  $R^3$ ,  $R^4$  et  $R^5$  représente  $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$  quand R représente un groupe alcanoyle contenant 1 à 4 atomes de carbone ou carbalcoxy contenant 2 à 6 atomes de carbone, et  $R^1$  et  $R^2$  ont la définition donnée ci-dessus;
  - ii) au moins l'un des symboles  $R^3$ ,  $R^4$  et  $R^5$  représente  $C_2H_5$  quand R est un atome d'hydrogène et  $R^1$  et  $R^2$  ont la définition donnée ci-dessus;
  - iii) quand deux des symboles  $R^3$ ,  $R^4$  et  $R^5$  représentent H, le symbole  $R^3$ ,  $R^4$  et  $R^5$  restant représente  $CH_3$ ,  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ , et R représente un groupe alcanoyle contenant 1 à 4 atomes de carbone ou carbalcoxy contenant 2 à 6 atomes de carbone, et  $R^1$  et  $R^2$  aient la définition donnée ci-dessus;
  - iv) quand R représente H, et  $R^1$  et  $R^2$  aient la définition donnée ci-dessus,  $R^1$  et/ou  $R^2$  représente (nt)  $NO_2$ ; ou
  - v) quand R représente H,  $R^1$  et  $R^2$  représente  $CF_3$  et  $R^3$  et  $R^5$  représentent  $CH_3$  et/ou H,  $R^4$  ne représente pas  $OCH_3$ .

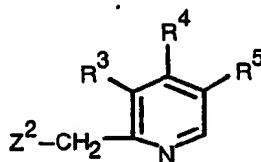
18. Composé selon la revendication 17, ou un sel thérapeutiquement acceptable de ce composé, dans lequel R représente H,  $R^1$ ,  $R^2$ ,  $R^3$  et  $R^5$  sont comme définis à la revendication 17, et  $R^4$  représente  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ .

19. Procédé pour préparer un composé selon l'une quelconque des revendications 17 et 18, par:
  - A. Réaction d'un composé de formule:



II

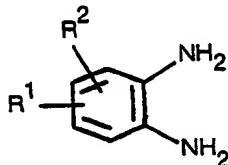
avec un composé de formule:



III

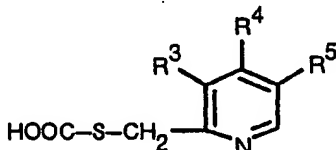
(formules dans lesquelles R,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont comme définis ci-dessus et l'un des symboles  $Z^1$  et  $Z^2$  représente SH et l'autre des symboles  $Z^1$  et  $Z^2$  est un groupe éliminable);

B. pour préparer un composé de formule I dans laquelle R représente H, la réaction d'un composé de formule:



IV

(dans laquelle  $R^1$  et  $R^2$  ont le même sens que celui indiqué ci-dessus) avec un composé de formule:

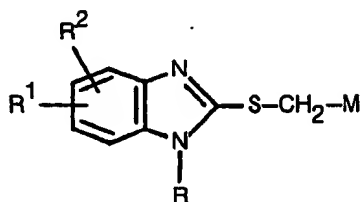


V

# 0 074 341

(dans laquelle  $R^3$ ,  $R^4$  et  $R^5$  ont le même sens que celui indiqué ci-dessus) pour former un composé de formule I dans laquelle R représente H;

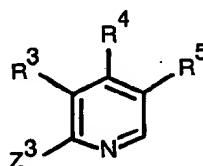
C. réaction d'un composé de formule:



VI

(dans laquelle R,  $R^1$  et  $R^2$  ont le sens indiqué ci-dessus et M représente K, Na ou Li) avec un composé de

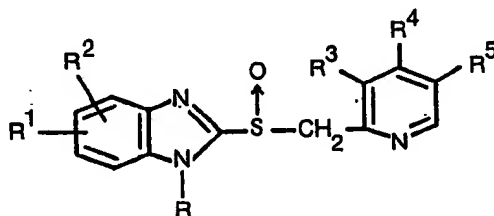
15 formule:



VII

25 (dans laquelle  $R^3$ ,  $R^4$  et  $R^5$  ont le sens indiqué ci-dessus, et  $Z^3$  est un groupe hydroxyle estérifié réactif) pour former un composé de formule I;

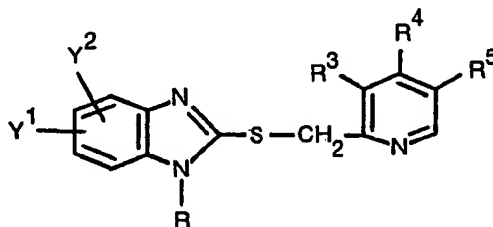
D. réduction d'un composé de formule:



VIII

pour former un composé de formule I;

40 E. pour préparer un composé de formule I, dans laquelle les radicaux  $R^1$  et/ou  $R^2$  représente (nt)  $\text{COOCH}_3$  ou  $\text{COOC}_2\text{H}_5$ , réaction d'un composé de formule:



IX

(dans laquelle R,  $R^3$ ,  $R^4$  ou  $R^5$  ont la définition donnée ci-dessus et  $Y^1$  représente  $-\text{COOH}$  ou un de ses dérivés ayant une réactivité équivalente, et  $Y^2$  représente  $-\text{COOH}$  ou un de ses dérivés ayant une réactivité équivalente, ou  $R^1$ ), avec



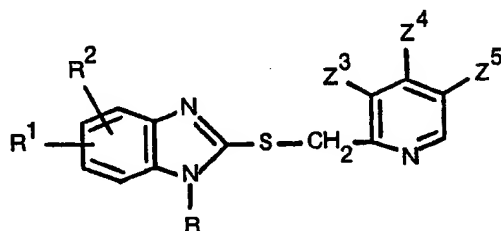
X



XI

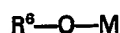
ou avec un dérivé ayant une réactivité équivalente) pour former un composé de formule I, dans laquelle  $R^1$  et/ou  $R^2$  représente (nt)  $\text{CH}_3\text{COO}$  ou  $\text{CH}_3\text{CH}_2\text{COO}$ ;

F. pour préparer un composé de formule I, dans laquelle l'un au moins des symboles  $R^3$ ,  $R^4$  et  $R^5$  représente  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ , réaction d'un composé de formule :



XII

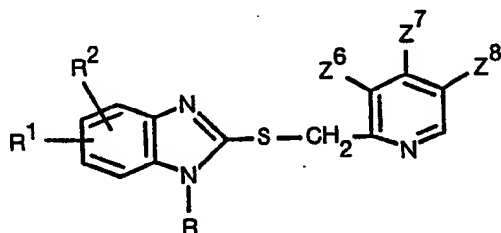
(dans laquelle  $R$ ,  $R^1$  et  $R^2$  sont tels que définis ci-dessus, et  $Z^3$ ,  $Z^4$  et  $Z^5$  représentent soit  $R^3$ ,  $R^4$  et  $R^5$ , respectivement, soit un halogène comme  $Cl$ ,  $Br$ ,  $F$  ou  $I$ , soit  $NO_2$ , l'un au moins des symboles  $Z^3$ ,  $Z^4$  et  $Z^5$  représentant un halogène ou  $NO_2$ ) avec un composé de formule:



XIII

(dans laquelle  $R^6$  représente  $CH_3$ ,  $C_2H_5$ ,  $CH_2CH_2OCH_3$  ou  $CH_2CH_2OCH_2CH_3$ , et  $M$  représente  $Na$ ,  $K$  ou  $Li$ ) pour former un composé de formule I dans laquelle l'un au moins des symboles  $R^3$ ,  $R^4$  et  $R^5$ , représente  $OCH_3$ ,  $OC_2H_5$ ,  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ ;

G. pour préparer un composé de formule I (dans laquelle au moins l'un des symboles  $R^3$ ,  $R^4$  et  $R^5$ , représente  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ ), réaction d'un composé de formule:



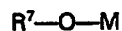
XIV

(dans laquelle  $R$ ,  $R^1$  et  $R^2$  sont tels que définis ci-dessus, et  $Z^6$ ,  $Z^7$  et  $Z^8$  représentent  $R^3$ ,  $R^4$  et  $R^5$ , respectivement, ou un radical:



XV

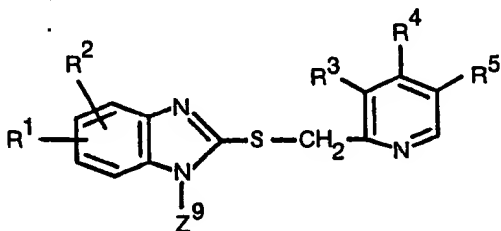
dans lequel  $Y$  représente un atome d'halogène, l'un au moins des symboles  $Z^6$ ,  $Z^7$  et  $Z^8$  représentant  $OCH_2CH_2Y$ ) avec un composé de formule:



XVI

(dans laquelle  $R^7$  représente  $CH_3$  ou  $CH_2CH_3$  et  $M$  représente  $Na$ ,  $K$  ou  $Li$ ) pour former un composé de formule I dans laquelle au moins l'un des symboles  $R^3$ ,  $R^4$  et  $R^5$  représente  $OCH_2CH_2OCH_3$  ou  $OCH_2CH_2OCH_2CH_3$ ;

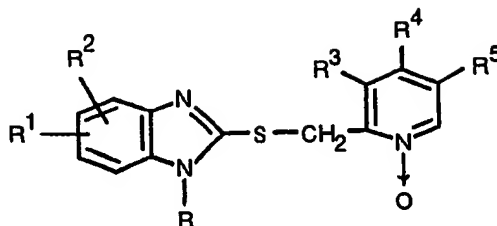
H. pour préparer un composé de formule I (dans laquelle  $R$  représente  $H$ ), hydrolyse d'un composé de formule:



XVII

(dans laquelle  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ci-dessus, et  $Z^9$  représente un groupe alcanoyloyle ou un groupe carboalcoxy) pour former un composé de formule I dans laquelle  $R$  représente  $H$ ;

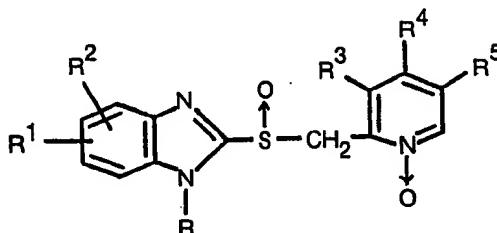
I. réduction d'un composé de formule:



XVIII

pour former un composé de formule I;

J. réduction d'un composé de formule:



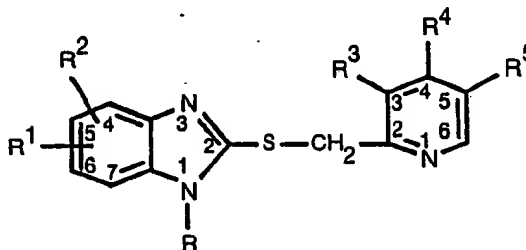
XIX

pour former un composé de formule I;

puis, si on le désire, on transforme le composé ainsi obtenu en un sel thérapeutiquement acceptable.

### 30 Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule:



et de ses sels pharmaceutiquement acceptables, [formule dans laquelle:

R<sup>1</sup> et R<sup>2</sup> sont identiques ou différents et sont choisis chacun dans l'ensemble constitué par H, CF<sub>3</sub>, NO<sub>2</sub>, —COOCH<sub>3</sub>, —COOC<sub>2</sub>H<sub>5</sub>, un groupe alkyle contenant 1 à 7 atomes de carbone, un atome d'halogène, un groupe alcoxy contenant 1 à 5 atomes de carbone et un groupe alcanoyle contenant 1 à 4 atomes de carbone;

R est choisi dans l'ensemble constitué par H, un groupe alcanoyle contenant 1 à 4 atomes de carbone et carboalcoxy contenant 2 à 6 atomes de carbone; et

R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, identiques ou différents, sont choisis chacun dans l'ensemble constitué par H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, à la condition que:

a) au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> soit choisi dans l'ensemble constitué par CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> et

b) quand deux des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représentent H, le radical R<sup>3</sup>, R<sup>4</sup> ou R<sup>5</sup> restant soit choisi dans l'ensemble constitué par OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> et OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>; et à la condition que:

i) au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représente CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub> quand R représente un groupe alcanoyle contenant 1 à 4 atomes de carbone ou carbalcoxy contenant 2 à 6 atomes de carbone, et R<sup>1</sup> et R<sup>2</sup> ont la définition donnée ci-dessus;

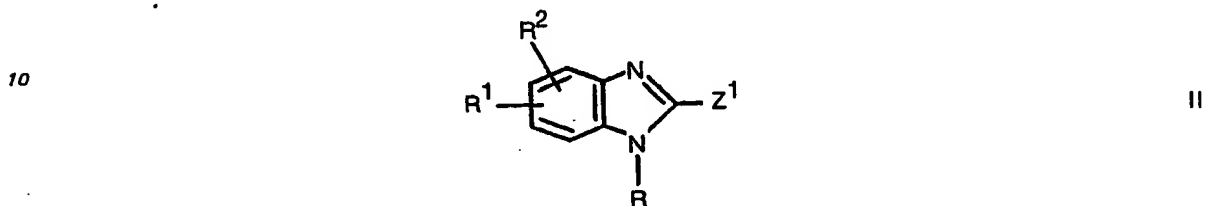
ii) au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représente C<sub>2</sub>H<sub>5</sub> quand R représente un atome d'hydrogène, et R<sup>1</sup> et R<sup>2</sup> ont la définition donnée ci-dessus;

iii) quand deux des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représentent H, le radical R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> restant représente CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, et R représente un groupe alcanoyle contenant 1 à 4 atomes de carbone ou carboalcoxy contenant 2 à 6 atomes de carbone, et R<sup>1</sup> et R<sup>2</sup> aient la définition donnée ci-dessus;

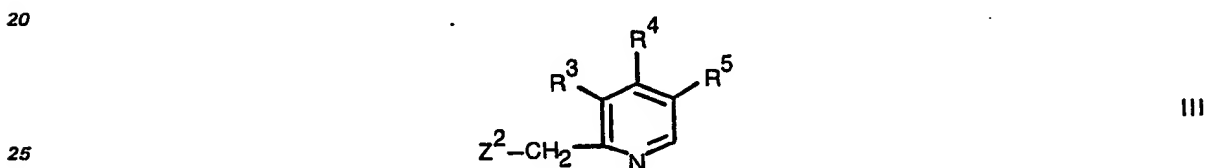
iv) quand R représente H, et R<sup>1</sup> et R<sup>2</sup> ont la définition donnée ci-dessus, R<sup>1</sup> et/ou R<sup>2</sup> représente (nt) NO<sub>2</sub>;  
ou

v) quand R représente H, R<sup>1</sup> ou R<sup>2</sup> représente CF<sub>3</sub> et R<sup>3</sup> et R<sup>5</sup> représentent CH<sub>3</sub> et/ou H, R<sup>4</sup> ne représente pas OCH<sub>3</sub>, par

5 A. Réaction d'un composé de formule:

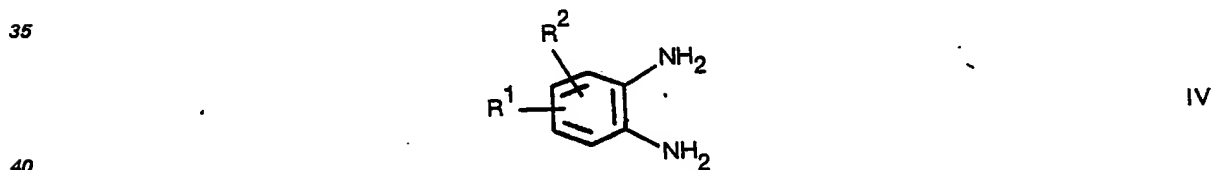


avec un composé de formule:



(formules dans lesquelles R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont comme définis ci-dessus et l'un des symboles Z<sup>1</sup> et Z<sup>2</sup> représente SH et l'autre des symboles Z<sup>1</sup> et Z<sup>2</sup> représente un groupe éliminable);

B. pour préparer un composé de formule I dans laquelle R représente H, la réaction d'un composé de formule:

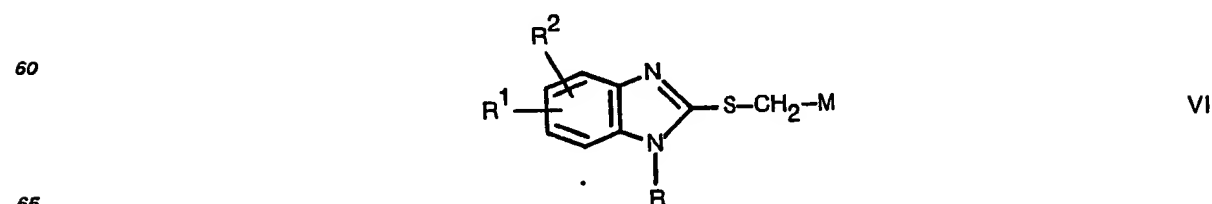


(dans laquelle R<sup>1</sup> et R<sup>2</sup> ont le même sens que celui donné ci-dessus) avec un composé de formule:



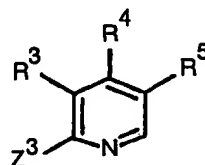
(dans laquelle R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> ont le même sens que celui indiqué ci-dessus) pour former un composé de formule I dans laquelle R représente H;

55 C. réaction d'un composé de formule:



(dans laquelle R, R<sup>1</sup> et R<sup>2</sup> ont le sens indiqué ci-dessus et M représente K, Na ou Li) avec un composé de formule:

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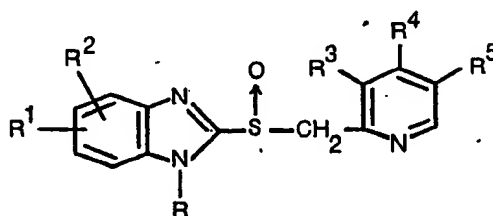
VII

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(dans laquelle R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> ont le sens indiqué ci-dessus, et Z<sup>3</sup> est un groupe hydroxyle estérifié réactif) pour former un composé de formule I;

D. réduction d'un composé de formule:

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VIII

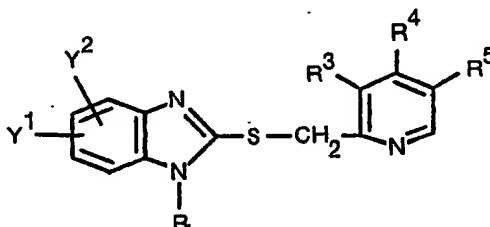
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pour former un composé de formule I;

E. pour préparer un composé de formule I, (dans laquelle les radicaux R<sup>1</sup> et/ou R<sup>2</sup> représente (nt) COOCH<sub>3</sub> ou COOC<sub>2</sub>H<sub>5</sub>), réaction d'un composé de formule:

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IX

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40 (dans laquelle R, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont comme définis ci-dessus et Y<sup>1</sup> représente —COOH ou un de ses dérivés ayant une réactivité équivalente, et Y<sup>2</sup> représente —COOH ou un de ses dérivés ayant une réactivité équivalente, ou R<sup>1</sup>), avec



X

45

ou

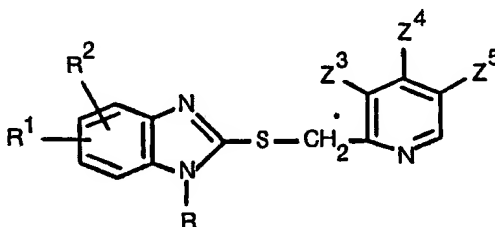


XI

50 ou un de leurs dérivés ayant une réactivité équivalente, pour former un composé de formule I dans laquelle R<sup>1</sup> et/ou R<sup>2</sup> représente (nt) CH<sub>3</sub>COO ou CH<sub>3</sub>CH<sub>2</sub>COO;

F. pour préparer un composé de formule I (dans laquelle au moins des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représente OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), réaction d'un composé de formule:

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XII

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65 (dans laquelle R, R<sup>1</sup> et R<sup>2</sup> sont comme définis ci-dessus, et Z<sup>3</sup>, Z<sup>4</sup> et Z<sup>5</sup> représentent soit R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>,

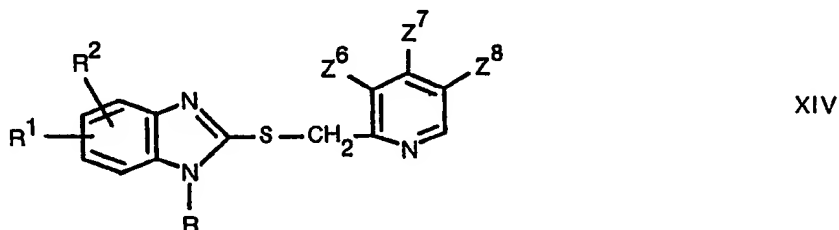
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respectiv ment, soit un halogène comme Cl, Br, F ou I, ou un groupe NO<sub>2</sub>, au moins des symboles Z<sup>3</sup>, Z<sup>4</sup> et Z<sup>5</sup> représentent un halogène ou NO<sub>2</sub>) avec un composé de formule:



(dans laquelle R<sup>6</sup> représente CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, et M représente Na, K ou Li) pour former un composé de formule I dans laquelle l'un au moins des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, représente OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>;

G. pour préparer un composé de formule I (dans laquelle au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, représente OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), réaction d'un composé de formule:



(dans laquelle R, R<sup>1</sup> et R<sup>2</sup> sont comme définis ci-dessus, et Z<sup>6</sup>, Z<sup>7</sup> et Z<sup>8</sup> représentent R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, respectivement, ou un radical:

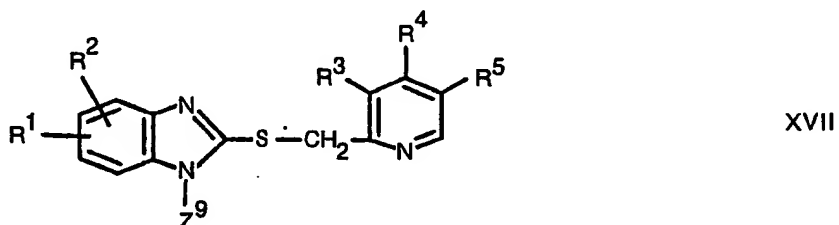


dans lequel Y est un atome d'halogène, l'un au moins des symboles Z<sup>6</sup>, Z<sup>7</sup> et Z<sup>8</sup> représentent QCH<sub>2</sub>CH<sub>2</sub>Y) avec un composé de formule:



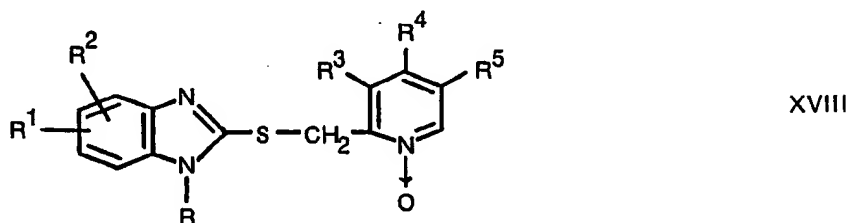
(dans laquelle R<sup>7</sup> représente CH<sub>3</sub> ou CH<sub>2</sub>CH<sub>3</sub>, et M représente Na, K ou Li) pour former un composé de formule I (dans laquelle au moins l'un des symboles R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représente OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>);

H. pour préparer un composé de formule I (dans laquelle R représente H), hydrolyse d'un composé de formule:



(dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont tels que définis ci-dessus, et Z<sup>9</sup> est un groupe alcanoyle ou un groupe carboalcoxy) pour former un composé de formule I, dans laquelle R représente H;

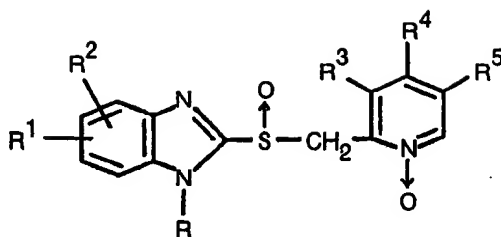
I. réduction d'un composé de formule:



pour former un composé de formule I;



J. réduction d'un composé de formule :



XIX

15 pour former un composé de formule I;

puis, si on le désire, on transforme le composé de formule I, ainsi obtenu, en un sel thérapeutiquement acceptable.

2. Procédé selon la revendication 1, pour la préparation d'un composé tel que défini à la revendication 1, ou d'un sel thérapeutiquement acceptable de ce composé, dans lequel R représente H; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>5</sup> sont comme définis à la revendication 1; et R<sup>4</sup> représente OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> ou OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>.